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A TRANSISTORIZED, SELF-CONTAINED, IMPLANTABLE PACEMAKER FOR THE LONG-TERM CORRECTION OF COMPLETE HEART BLOCK

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ELECTRICAL pacing of the heartbeat has been very effective in the management of atrioventricular block complicating the surgical repair of septal defects. A myocardial electrode wire[14] brought out through the chest wall at the time of operation requires only small voltages and eliminates the unpleasant side effects associated with the pacemaker originally described by Zoll,[15] who used rather high voltages delivered through skin electrodes.

It seemed logical to extend the indications for the use of a pacemaker to include frequent Stokes-Adams seizures in patients in whom the block, most often the residual effect of coronary occlusion, cannot be controlled by drugs. However, electrical stimulation of the heart on a permanent basis presents serious problems related in part to the artificial pacemaker but arising chiefly from the electrode.

An externally applied device, albeit a small and portable one linked to the myocardium by a wire traversing the skin, represents to some degree a hazard, an inconvenience, and a potential portal of entry for infection. An implantable pacemaker would obviate these difficulties. Glenn and Mauro[3] recently reported the clinical use of radiofrequency waves transmitted through the intact skin to a subcutaneously implanted receiver. An implanted and battery-driven pacemaker was mentioned by Senning.[10] A coil placed around the patient was used to recharge the batteries by induction.

The artificial pacemaker to be described was designed by one of us (W. G.). The objective was to provide a self-contained unit of small size, carrying its own

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power supply, and lasting long enough to make subcutaneous implantation practical and justifiable.

DESCRIPTION OF THE PACEMAKER

The pacemaker, including batteries, measures 6 cm. in diameter and 1.5 cm. in thickness. The circuit, transistorized, contains only 8 components. It is

Fig. 1.—Photograph of pacemaker assembly embedded in epoxy resin.

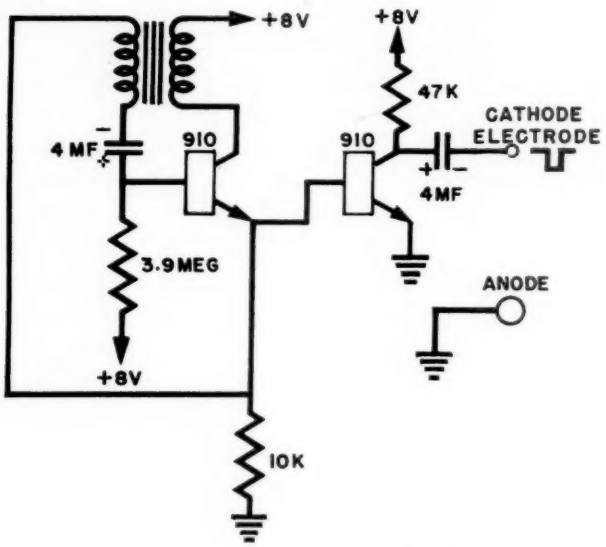

Fig. 2.—Circuit diagram of pacemaker.

a blocking oscillator, generating a very low-power pulse which in turn triggers a second transistor. The latter acts as a switch, draining a capacitor charged from the power supply. The capacitor then delivers a 1 msec. pulse to the

electrodes. The wave shape of the pulse is biphasic, with a positive and a negative peak. The peaks of opposing polarity are not symmetrical, but the areas under both curves are of equal size. Thus, there is no net transfer of electrons from the electrode into the tissue and this may be of importance in the prevention of injury to the tissues from long-continued stimulation.

The unit depicted in Fig. 1 delivers 8 v., but up to 15 v. could be obtained without an undue increase in dimensions. The mercury cell batteries,* are rated at a minimum of 450 Ma. hours and have a shelf life of 10 years. Since the current drain of the unit is only 11 μa, 5 years is a conservative estimate of its period of usability. Exhaustion of the battery supply is signaled by a slow rise in the pulse rate taking place over a period of weeks so that ample warning is given. The pulse rate is fixed once the unit has been assembled and it is set for each device by selection of an appropriate value for the 3.9 megohm resistor (Fig. 2).

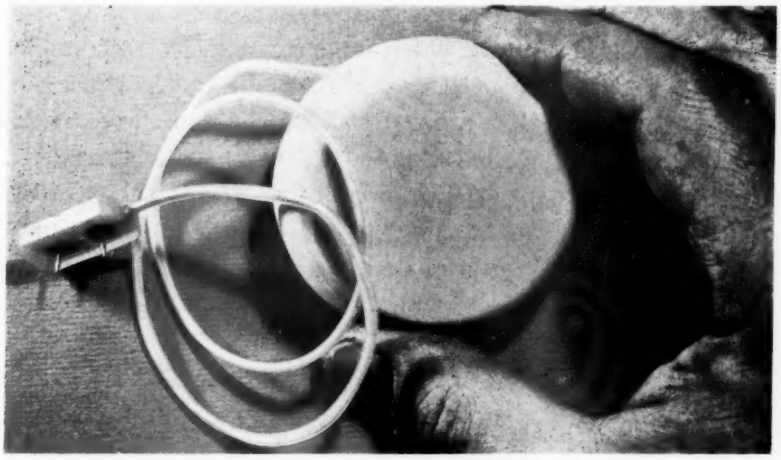

Fig. 3.—Photograph of finished pacemaker and electrode (bipolar patch electrode, Medtronics, Inc., Minneapolis, Minn.).

The entire assembly, including the batteries, is potted in epoxy resin† in order to eliminate motion between components and breakage of wires and solder points, as well as shorting in the circuit due to seepage of body fluids. The unit is then encapsulated in a second thin shell of Dow-Corning silicone rubber (RTV 502).‡

Thirty units of this general type have been experimented with over the past 18 months. Early units were protected only by a thin outer plastic capsule and disruption of the seal with ingress of body fluids was an occasional cause of electrical failure. The last 14 units (Fig. 3) have been completely embedded and some of these have been under observation for more than 12 months. Since this technique was adopted, no failures have been encountered from the pacemaker itself.

*Developed for this application by P. R. Mallory & Co., Inc., Indianapolis, Ind.
†Scotch Cast No. 5, Minnesota Mining & Mfg. Co., St. Paul, Minn.
‡Dow-Corning Center for Aid to Medical Research, Midland, Mich.

EXPERIMENTAL OBSERVATIONS

The main difficulties in long-term pacing have arisen from the electrodes. Most reported work in this field concerns unipolar electrodes as described by Weirich[14] and others.[1] The active electrode usually consists of the bared tip of an insulated wire buried in the myocardium. The indifferent electrode may be a similar wire or a small metal plate placed subcutaneously or elsewhere in the body. While this is perfectly satisfactory for a period of several weeks, there is, however, a gradual rise in the amount of current needed to initiate contraction. Also, resistance of the tissues around the electrode increases, so that higher and higher voltages are required to achieve the necessary current flow. As soon as voltage levels of from 15 to 20 v. are needed, there is twitching of the thoracic musculature and, finally, cardiac contraction cannot be obtained at tolerable voltage levels.

This sequence of events appears to be caused by scar formation around the electrode. Since this tissue is relatively avascular, it acts as an insulator. It also increases the physical distance which separates the electrode from the closest intact myocardial fiber capable of response to stimulation. Thus, a higher current density must be achieved at a greater distance from the electrode while at the same time the resistance of the tissue to current flow has increased. This rise in threshold, at least in our experience, was not related to the electrical stimulation itself. It has occurred to the same degree and as rapidly when stimulation was continuous as when it was intermittent, or when thresholds were determined at intervals with electrodes which were implanted but not used for stimulation at all.

Complete atrioventricular block was induced in dogs by the suture method of Starzl and Gaertner.[11] A wide variety of unipolar myocardial electrodes, including endocardial electrodes incorporated in a cardiac catheter,[2] were used. Regardless of modifications in shape, size, or placement, a rapid rise in threshold was seen, reaching unusable levels within 30 to 40 days. The upper graph in Fig. 4 is representative of some of our disappointing experiences with monopolar electrodes.

In August, 1959, we received a preliminary report by Hunter and Roth[4, 5] on a bipolar electrode.* The active and indifferent electrodes were 2 stainless steel prongs, 0.5 cm. in length, emerging from the surface of a small, flat silicone rubber patch. The patch was placed on the right ventricular surface and the 2 prongs, 1 cm. distant from each other, penetrated the myocardium. Observations were made on several dogs without induced atrioventricular dissociation for periods of up to 9 months and on 1 patient for 4 months. Threshold levels observed ranged from 4 to 14 Ma. with an impedance of approximately 1,000 ohms. Complete stability of the threshold levels had been reached in all cases after 3 to 4 weeks and since 14 Ma. against 1,000 ohms could be delivered with 14 v., it appeared that the modifications of Hunter and Roth offered promise for a solution to the vexing electrode problem.

*Commercially available through Medtronics, Inc., Minneapolis, Minn.

The results in our laboratory confirmed their observations in regard to a lower and more stable threshold with bipolar electrodes. The latter were implanted into the right ventricular myocardium of 6 dogs and thresholds were determined at intervals by externally placed pacemakers equipped with an

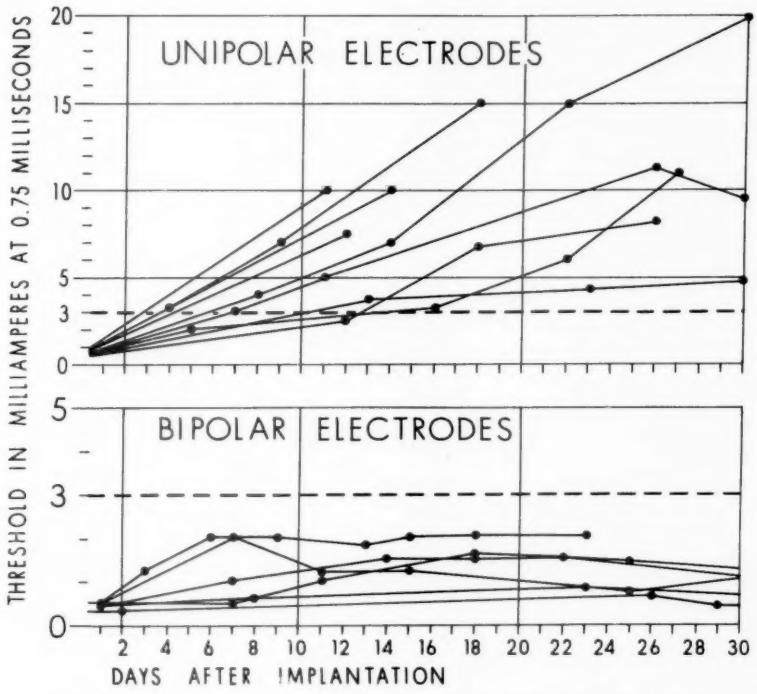

Fig. 4.—Comparison between threshold currents with unipolar electrodes and bipolar electrodes in dogs with surgically induced atrioventricular block.

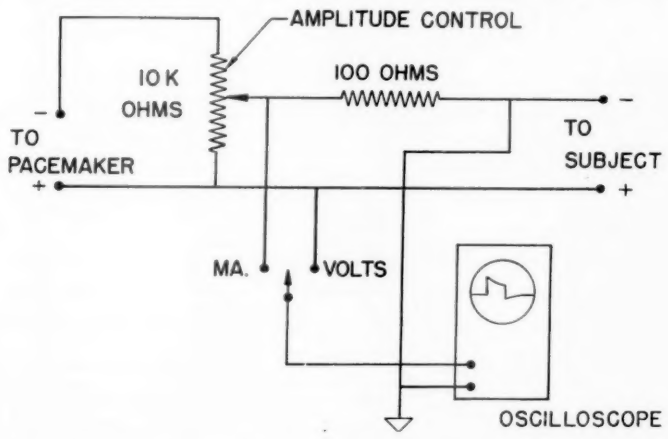

Fig. 5.—Circuit arrangement used for external pacemaker, permitting easy readings of threshold current and voltage on oscilloscope.

amplitude control and a slightly modified circuit (Fig. 5), permitting an easy reading of voltage and current to be made on an oscilloscope. Thresholds observed in 3 animals in which a complete block had been successfully induced were stable and ranged within approximately 2 Ma. (Table I). Higher currents were required in 3 animals without atrioventricular block (Fig. 6). This was

well demonstrated by the sudden rise in threshold in 2 of these dogs in which a normal rate spontaneously returned some time after induction of the block, presumably because of incomplete destruction of the conduction bundle (Fig. 6). The currents required to drive these normal hearts at supranormal rates ranged from 4 to 12 Ma., in line with Hunter's observations which also had been made on animals with normal heart rates.

In an additional 5 animals, a modification of the biopolar patch electrode was used. Teflon-covered stainless steel wires* were stripped of insulation over

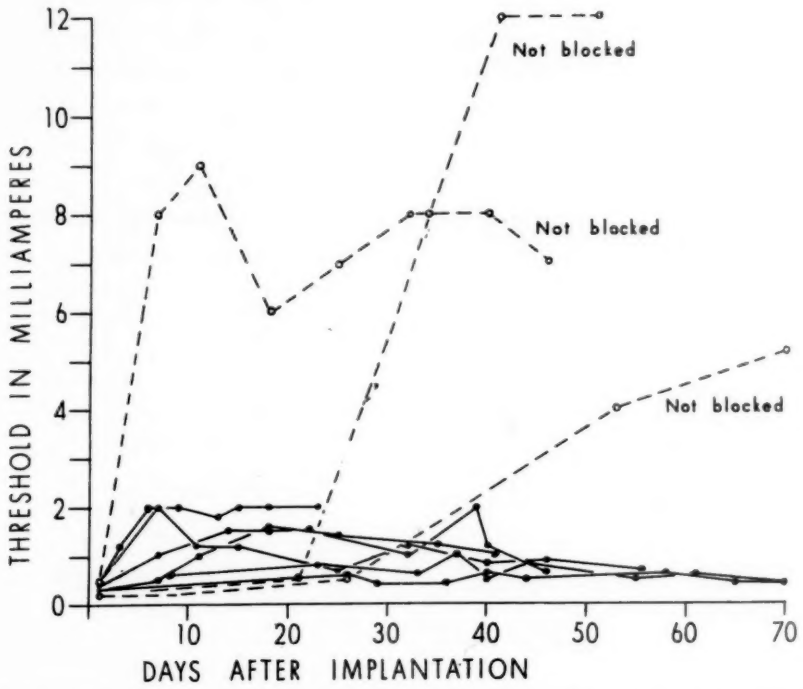

Fig. 6.—Comparison between high threshold currents needed to pace 3 normal dog hearts and low requirements of 6 dog hearts with induced atrioventricular dissociation. Bipolar electrodes (patches or wires) were used in both groups. Surgical induction of the block was initially successful in 2 animals but a normal rate spontaneously returned after approximately 21 and 26 days, respectively.

the terminal centimeter. Just proximal to the bared portion, a knot was tied in the wire. The wires were then pushed into the myocardium, 1 cm. from each other, up to the level of the knot. Anchorage was secured by suturing the pericardium to the epicardium around the knot. Thresholds with this technique were somewhat lower than with the patch. In 1 animal (Table II, 19-N), the initial threshold after induction of the block was 0.5 Ma. Continuous stimulation with an implanted pacemaker was then carried out and the device removed after 123 days. The threshold was then found to be 1.5 Ma., requiring 2 v. to drive the heart (Table II). Since the threshold currents are the crux of the problem of long-term pacing, whether an implantable or an external device is contemplated, and because average values are not meaningful in this situation, detailed observations on current, voltage, and impedance are given in Tables I and II.

*Commercially available through Medtronics, Inc., Minneapolis, Minn.

TABLE I. THRESHOLD DETERMINATIONS* ON 3 DOGS WITH SURGICALLY INDUCED COMPLETE ATRIOVENTRICULAR DISSOCIATION AND BIPOLAR PATCH ELECTRODE IMPLANTED INTO THE RIGHT VENTRICULAR MYOCARDIUM

DOG NO.	DAYS†	CURRENT (Ma.)	VOLTAGE (V.)	IMPEDANCE (THOUSAND OHMS)
90-N	1	0.4	1.0	2.5
	7	1.0	1.0	1.0
	14	1.5	1.5	1.0
	18	1.5	1.5	1.0
	22	1.5	2.0	1.3
	32	1.0	1.5	1.5
	39	2.0	2.0	1.0
	40	1.2	1.5	1.3
	46	0.6	1.0	1.7
	68	1.0	2.0	2.0
	73	1.5	2.6	1.3
67-M‡	1	0.5		
	3	1.2		
	6	2.0		
	9	2.0	4.0	2.0
	13	1.8	4.0	2.2
	16	2.0	5.0	2.5
	17	2.0	5.0	2.5
	18	2.0	5.0	2.5
	21	1.5	5.0	3.3
44-O‡	1	0.5	1.0	2.0
	30	3.0	2.4	0.8
	38	2.0	1.5	0.8

*Thresholds were determined with an external pacemaker.

†Number of days after implantation of electrode.

‡In animals No. 67-M and 44-O an internal device was implanted for continuous pacing on the twenty-first and thirty-eighth days, respectively. Both animals are being kept for long-term observations and thresholds will be determined at yearly intervals.

In summary of the experimental data, it may be stated that the use of a bipolar electrode for pacing the heartbeat in animals with induced atrioventricular block has led to low and stable threshold currents. The use of 2 single wires buried in the myocardium has yielded a further reduction in threshold, although the mechanical stability of this method of fixation compares unfavorably with that of the more solid patch. Threshold levels have remained stable well beyond the initial 4-week period during which a rise had invariably been observed when unipolar electrodes were employed. A clinical trial of the method in selected cases of chronic and symptomatic atrioventricular block appears justified and might best be carried out in 2 stages.

During the first stage, a bipolar patch is placed onto the right ventricular myocardium. An approach through the bed of the fifth costal cartilage is adequate for this. The electrode wires are brought out through the chest wall and the heartbeat is paced with an external device, the rate and amplitude of which can be controlled. Thresholds are then determined at intervals and a period of observation of from 4 to 6 weeks should be sufficient to ascertain their stability. At the second stage, an implantable pacemaker, the power of which exceeds the minimum requirements by a wide margin, is substituted. This is accomplished by soldering the 2 electrode wires to the terminals of the implantable device and by covering the area of this junction with silicone rubber. This compound sets

within minutes, cures at room temperature, and provides a firm bond between the silicone rubber capsule of the pacemaker and the silicone sleeve surrounding the 2 Teflon wires. The entire assembly is then sterilized on the outside of the body. A variety of skin antiseptics have been found to be suitable for this purpose. Implantation into a subcutaneous pocket can then be carried out with local anesthesia.

TABLE II. THRESHOLD DETERMINATIONS ON 5 ANIMALS WITH SURGICALLY INDUCED COMPLETE ATRIOVENTRICULAR ASSOCIATION AND IMPLANTED BIPOLAR WIRE ELECTRODE

DOG NO.	DAYS*	CURRENT (Ma.)	VOLTAGE (V.)	IMPEDANCE (THOUSAND OHMS)
17-N	8	0.6	0.8	1.3
	23	0.8	1.6	2.0
	33	0.6	2.0	3.3
	37	1.0	2.0	2.0
	40	0.5	1.8	3.6
	44	0.8	2.0	2.5
	54	0.5	2.0	4.0
	61	0.6	2.0	3.3
	70	0.4	1.2	3.0
	75	1.2	2.0	1.7
	97	1.0	2.0	2.0
	101	1.0	2.2	2.2
	110	1.0	2.2	2.2
82-N	1	0.5	0.4	0.8
	7	0.5	0.6	1.2
	11	1.0	0.6	0.6
	18	1.6	0.8	0.5
	25	1.4	0.8	0.6
	35	1.2	1.0	0.8
	41	1.0	0.7	0.7
	63	1.0	2.0	2.6
28-M	1	0.5	0.5	1.0
	7	2.0	1.0	0.5
	11	1.2	1.0	0.9
	15	1.2	0.8	0.7
	25	0.7	0.5	0.7
	32	1.2	0.6	0.5
	40	0.8	1.2	1.5
	46	0.9	2.3	2.6
	56	0.6	1.2	2.0
15-N	2	0.3	0.4	3.0
	26	0.6	3.0	5.0
	29	0.4	2.0	5.0
	36	0.4	2.0	5.0
	40	0.6	1.5	2.5
	44	0.5	1.5	3.0
	58	0.6	2.2	3.3
	65	0.4	1.2	3.0
	75	0.4	1.2	3.0
	81	0.4	1.4	3.5
	91	0.3	1.5	5.0
	103	0.8	3.0	3.8
	126	0.5	2.4	5.0
	150	0.5	2.4	5.0
19-N†	1	0.5	0.5	1.0
	123	1.5	2.0	1.4

*Number of days after implantation of electrode.

†Heartbeat in animal 19-N was paced continuously by an implanted device which was removed after 123 days for threshold determination.

If, after several years, exhaustion of the batteries is heralded by a slow rise in the pulse rate, the pacemaker can be replaced in the subcutaneous location without disruption of the myocardial electrode. Final subcutaneous implantation has, at the time of this writing, not been performed in patients.

Implantation of a bipolar patch electrode has been made in 1 patient and the unit has been used as an external device for 5 weeks. He was a 65-year-old man with a pulse rate varying from 26 to 30, who had sustained innumerable Stokes-Adams attacks, with as many as 20 episodes a day. Rates of 50 and 60 were used for pacing and no further attacks were observed with either of these rates. The man was ambulatory. Thresholds were determined on 23 separate occasions. Initially, 0.5 Ma. and 1 v. were required. The level reached a maximum of 3.5 Ma. and 3 v. on the twelfth day and after that it slowly fell to 1.5 Ma. and stabilized at 1.2 Ma. The patient suddenly died on the thirty-fifth postoperative day. The pacemaker and the electrodes were checked immediately and were found to be in proper working order. Tissue impedance at the electrode had not changed. The autopsy findings supported the conclusion that the patient had suffered another coronary occlusion.

DISCUSSION

A detailed description of the clinical features and course of complete heart block can be found in the reviews of substantial case series made by Penton, Miller, and Levine[7] and by Rowe and White.[9]

Briefly, it is generally agreed that congenital block, not associated with other anomalies, is relatively well tolerated. Treatment of the atrioventricular block appearing during or after surgical repair of septal defects is now well standardized. More frequently than not, this type of dissociation will spontaneously relent so that only temporary pacing may be needed.

The clinical course of permanent atrioventricular block after operation is not as well documented. If repair of the defect has been achieved, one might expect the residual block to create a situation analogous to that obtaining in pure congenital atrioventricular block, that is, the residual block would be well tolerated. However, this seems not to be entirely true and the outlook in such cases is said to be less favorable.[6] If further evidence corroborates this impression, an attempt at long-term pacing may be indicated for permanent block after an otherwise successful repair of a congenital defect.

Acquired atrioventricular block in adults is most often due to coronary thrombosis. When the atrioventricular dissociation appears during an acute occlusion, it carries a grave prognosis since the cardiac output, reduced by the infarction, falls to even lower levels because of the slow rate. Compensatory adjustment by an increased stroke volume requires time to develop and maintenance of a satisfactory rate through use of medication or a pacemaker is urgently indicated. If an external pacemaker with skin electrodes is tolerated by the patient, this method is obviously preferable since the block in this acute phase is most often intermittent and transient.[7, 9] An external pacemaker permits the use of a monitoring device so that stimulation can be limited to periods when the rate is low. If stimulation through

skin electrodes is intolerable to the patient, either the percutaneous introduction of a myocardial wire as described by Ross and associates[8] and by Thevenet and colleagues[13] or the use of an endocardial electrode through an indwelling cardiac catheter as reported by Furman and his group[2] may permit temporary pacing without the risk of thoracotomy.

When atrioventricular block occurs during the chronic phase of coronary disease, its onset may be manifested by a Stokes-Adams attack but, more often, its beginning is quite insidious and transient at first. Once Stokes-Adams attacks have occurred, the block is likely to be permanent in such cases. In the majority of instances, the slow rate is well tolerated and insertion of permanent electrodes through a thoracotomy should be limited to those patients in whom a chronic and nonintermittent block is refractory to control by drugs and severely disabling either because of repeated Stokes-Adams attacks or because rate and cardiac output are so low that not even the requirements of very modest physical efforts can be met.

The rate of stimulation as well as the fact that it cannot be varied with the above-described device (at least in its present stage of development) warrants some discussion. We have come to believe that the objective should be a rate just fast enough to prevent disabling attacks and to permit very moderate physical activity. In all likelihood, a rate between 40 and 50 beats per minute should be satisfactory in nearly all instances and disabling symptoms are rarely observed in patients in whom the rate does not fall considerably below these levels. In fact, it has been observed that anginal attacks are very rare in patients with heart block and it may well be that the mechanics and efficiency of coronary flow and cardiac work in the presence of some coronary obstruction are favorably influenced by the low rate. Furthermore, the limitations imposed upon physical activities in patients with slow rates may be actually beneficial. Rowe and White[9] found that patients with Stokes-Adams syndrome survived more than twice as long from the onset of atrioventricular dissociation as those in whom it did not produce attacks.

An objection may be raised to the fixed rate of the implanted pacemaker and, on purely theoretical grounds, it may appear to be preferable to have a device in which the rate is controlled by the auricular pacemaker as described by Stephenson and associates[12] for the treatment of postoperative block. However, this would require fairly elaborate monitoring and control mechanisms to prevent the artificial pacemaker from following the auricular rhythm if it ever became abnormal. The deleterious effects of various arrhythmias upon coronary hemodynamics are well known. Also, since clinical evidence suggests that subnormal rates are quite well tolerated provided they do not fall to levels at which an adequate diastolic pressure cannot be maintained, it seems that the simplicity of an implantable device with a fixed pace outweighs the theoretical disadvantages resulting from the loss of adjustability of the rate.

CONCLUSIONS

1. A transistorized, self-contained, implantable pacemaker with an expected 5-year period of usability has been described.

2. Observations on a bipolar patch electrode and a modification thereof have been presented and show that threshold currents required to drive the heart are low and stable enough to make implantation practical.

3. The indications for prolonged pacing in selected cases of permanent, nonintermittent, and disabling atrioventricular dissociation have been discussed.

ADDENDUM

Since submission of this manuscript, subcutaneous implantation of the pacemaker has been accomplished in 3 patients. The first was a 77-year-old man who had been in complete heart block for several years. His idioventricular rate was 32 and he had sustained numerous

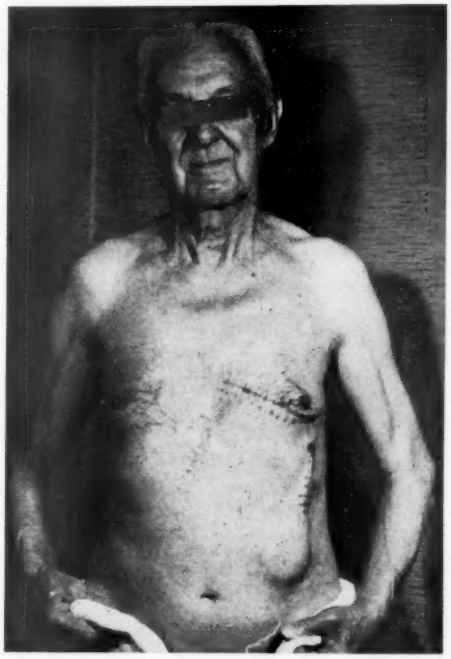

Fig. 7.—Photograph of patient with subcutaneously implanted pacemaker. The device is in the subcutaneous abdominal tissues and the site of implantation is indicated by the slight protrusion below the abdominal skin incision.

falls and a skull fracture caused by Stokes-Adams attacks. On April 18, 1960, a bipolar myocardial electrode was inserted and his heartbeat has been continuously paced since. He had been observed for several weeks while an external device was employed. The stimulation threshold stabilized at 3 Ma. On June 6, 1960, an internal pacemaker was implanted into the subcutaneous tissues of the abdomen (Figs. 7 and 8).

The second and third patients were women, 57 and 65 years of age, respectively, and both had been in complete heart block for approximately 1 year. Both had had numerous Stokes-Adams attacks and in the older patient, one episode of unconsciousness had lasted for 24 hours. Both have had continuous external pacing since the latter part of April and the thresholds stabilized at 2.2 and 3 Ma., respectively. Subcutaneous pacemakers were then substituted.

In the oldest patient, a rate of 46 was used and in the others, a rate of 60 was employed. All 3 patients have made completely uneventful recoveries. No complications have been encountered. A marked decrease in the size of the heart was observed in all patients and there has been a marked improvement in their well-being. The younger of the 2 female patients has returned to work. We believe these 3 cases to be the first recorded successful instances of correction of a physiologic disorder by an implanted and self-contained electronic device carrying its own source of power.

An additional 5 patients have been operated upon more recently and are still under observation with an external pacemaker. With the exception of a minor superficial wound infection in one, there have been no complications. Thresholds are stable and low and substitution of an internal device is contemplated in the near future. Detailed case reports are in preparation and will be the subject of another publication.

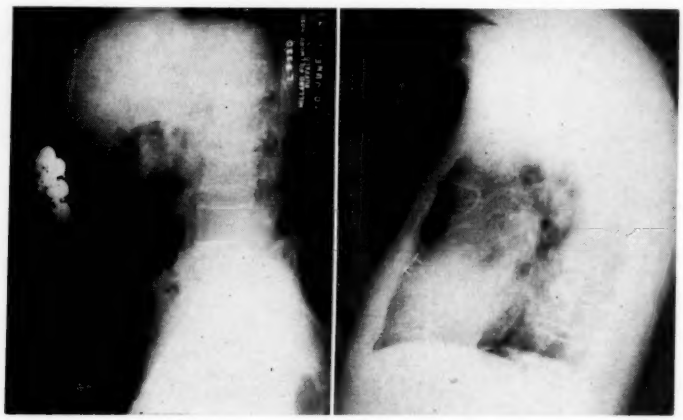

Fig. 8.—Roentgenograms of patient with subcutaneously implanted pacemaker.

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QUANTITATIVE ASSESSMENT OF EXTENT OF GASTRIC RESECTION

Comparison of Pattern-Planimeter and Pattern Weight Methods

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FOR a number of years it has been the practice of the Department of Surgery of the University of Washington to obtain objective measurements of the extent of gastric resection at the time of operation. This has been accomplished by obtaining patterns of the residual stomach by means of a sheet of Cottonoid which is pressed against the flattened surface of the stomach and later trimmed as necessary. A similar pattern is made from the resected portion of stomach immediately after operation. These Cottonoid patterns are then used (when dry) to trace on a sheet of paper the outline of both residual stomach and resected stomach for measurement with a polar planimeter.[1-3] Briefly, the polar planimeter (Keuffel and Esser Co.) is a simple instrument for the accurate measurement of plane areas of any form. To measure an area it is only necessary to run a tracer point around the periphery of the figure and read the distance which a measuring wheel has revolved during the process. From the ratio of the areas of the resected stomach pattern and the total stomach pattern, one can readily determine the percentage of the total area excised.

It occurred to one of the authors (Dr. Harkins) that one might determine the per cent resection just as readily with less specialized instruments, by obtaining the weights of the 2 paper patterns traced from the Cottonoid patterns taken at operation. The preliminary steps are the same. One obtains the 2 Cottonoid patterns at operation and traces their outlines on paper. Instead of measuring the area by polar planimetry, one merely weighs the 2 patterns which are cut out of a single piece of standard bond paper or other paper of constant consistency or texture. From the weight ratios of these pattern cut-outs one can then determine the per cent resection.

For this study the Cottonoid patterns from 10 patients with gastric resection were used. In each instance the 2 pattern outlines were traced upon a single sheet of bond stationery paper and the areas determined by polar planimetry. Six separate patterns were cut out for each Cottonoid pattern. Three patterns were cut from standard bond stationery paper and 3 from a standard canary backing or "second" paper, in order to determine the consistency of weight results with different types. All 6 cut-out patterns were weighed individually. The percentage of stomach resected was determined on the basis of the pattern weight ratios (Table I).

In each instance, the "per cent resection" figure was the same or within 1 per cent of the figure obtained with polar planimetry (Table II). Also of

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TABLE I. PER CENT RESULTS OF DETERMINATIONS IN ONE CASE OF GASTRIC RESECTION

PATTERN NO.	WEIGHT OF RESIDUAL STOMACH PATTERN (GM.)	WEIGHT OF RESECTED STOMACH PATTERN (GM.)	TOTAL STOMACH PATTERN WEIGHT (GM.)	PER CENT RESECTION DETERMINED BY PATTERN WEIGHT RATIOS*
Standard Bond Paper.†				
1	.75	.84	1.59	53
2	.88	1.00	1.88	53
3	.75	.85	1.60	53
Canary Backing Paper.†				
4	.73	.83	1.56	53
5	.69	.78	1.47	53
6	.72	.81	1.53	53

* $\frac{\text{Resected pattern weight}}{\text{Total pattern weight}} \times 100 =$ per cent resection (expressed as nearest whole per cent).

†A separate sheet of paper was used in each of the 3 pattern weight measurements.

note was the consistency of percentage results with the 2 types of paper and between individual sheets of the same type of paper if both resected and residual stomach patterns were cut out of the same sheet (Table I). The initial weights were obtained on a Mettler semimicro single pan (analytical) scale that records weight accurately to the nearest tenth of a milligram. However, it was found that any simple laboratory scale that weighs accurately to the nearest one-hundredth of a gram would also give results within 1 per cent of the figure obtained with planimetry, and a scale that measures accurately to the nearest tenth of a gram would give results within 4 per cent of the figure obtained with planimetry. Therefore one has a readily available means of objectively checking his estimate of per cent resection at operation, for the necessary materials are available in any laboratory.

It is not the purpose of this paper to point out the great need for objective measurements of estimated partial gastrectomies. It is sufficient to say that any comparison or evaluation of results of operations for ulcer disease is impossible without as accurate information as can be obtained concerning the true amount of stomach resected. It is hoped that this extremely simple method of objective measurement of the degree of gastric resection will encourage more individuals to check their subjective estimates with more objective figures.

TABLE II. COMPARISON OF ESTIMATES OF EXTENT OF RESECTION

PATIENT	PER CENT RESECTION BY SURGEON'S ESTIMATE	PER CENT RESECTION BY POLAR PLANIMETRY	PER CENT RESECTION BY PATTERN WEIGHT RATIOS
1	50	54	53
2	50	50	50
3	50	44	44
4	75	76	76
5	75	80	81
6	60	71	71
7	70	71	71
8	60	61	61
9	50	57	57
10	50	55	56

SUMMARY

1. A simplified means of obtaining objective measurements of the extent of gastric resection, which includes the necessary consideration of the size of the residual stomach, was applied in 10 cases of gastric resection.

2. The results obtained by the pattern weight method were comparable and consistent with those obtained by polar planimetry.

3. It would appear that any type of paper of reasonably constant consistency (standard bond stationery paper) is suitable for the pattern weight studies if both resected and residual stomach patterns are cut from the same sheet of paper.

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PARTIAL GASTRECTOMY FOR CHRONIC DUODENAL ULCER

Results of Follow-up in 700 Cases

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A RE-EVALUATION of an accepted surgical procedure for the treatment of chronic duodenal ulcer is important. This report concerns 700 consecutive and unselected patients* upon whom a partial gastrectomy was performed.

The operations were carried out over a 12-year period under the direct guidance and supervision of the same Chief of the Surgical Service (L. T. P.), and his staff who were trained by him.

This series is unique in other ways. The follow-up was adequately recorded in 86 per cent of the patients by a uniformly controlled follow-up system and program with thorough laboratory and clinical evaluations. The same uniform control was applied to the method of selection for operation, surgical technique employed, and postoperative care of the patients.

Through repeated studies of this type made over a long period of time, we are able to establish more carefully and more completely certain basic tenets. These may either prove the merits of this operation or reveal certain undesirable features which could outweigh the basic premise, and provide the surgeon with the facts necessary for his final acceptance or rejection of this operation.

The primary reason for this report is to present our results with partial gastrectomy. The selection of patients for surgical intervention was based upon the universally accepted criteria of hemorrhage, perforation, obstruction, recurrent ulceration, and intractability. This report concerns 700 patients treated by partial gastrectomy for chronic duodenal ulcer on the Surgical Service of this hospital from Aug. 1, 1946, to Aug. 1, 1958.

Age Incidence.—The average age was 47.3 years. The youngest patient was 21 and the oldest was 81 years of age. The greatest number, 54 per cent, were in the 40 to 59 year age group. However, 17.7 per cent were over 60 years old (Table I).

Duration of Symptoms and Preoperative Complications.—The average duration of symptoms prior to resection was 11.1 years. As usual, there were a great number of complications. The 2 most common ones were intractability and/or gastrointestinal bleeding. The patients with bleeding totaled 450 (64.3 per cent). In 175 of these (25 per cent) the bleeding was considered to be massive, in 113 (16 per cent) it was moderate, and in 162 (23 per cent) it was classified as minimal. In general, operations in the latter group were elective procedures.

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*These patients will be included in a cooperative peptic ulcer study which the Veterans Administration Research in Surgery Program is conducting.

TABLE I. AGE DISTRIBUTION

AGE	NO.	%
20-29	70	10.0
30-39	128	18.3
40-49	134	19.0
50-59	244	35.0
60-69	108	15.4
70-79	14	2.0
80-89	2	0.3
Totals	700	100

Perforation had occurred in 112 (16 per cent) and in several it had occurred more than once. As shown in Table II, many previous surgical procedures had been performed as a result of these complications.

TABLE II. PREVIOUS SURGICAL PROCEDURES

TYPE	NO.	%
Gastroenterostomy	27	3.85
Gastrectomy, partial	14	2.0
Perforated ulcer, closure	112	16.0
Reresection	2	0.28
Cholecystectomy	48	6.85
Splenectomy	4	0.57
Vagectomy, partial, left	1	0.14
Total	208	29.7

Preoperative Gastrointestinal Bleeding.—Gastrointestinal bleeding is probably the most serious of the complications of duodenal ulcer (Table III). In this survey are included all of the cases in which bleeding occurred. As noted previously, 450 (64.3 per cent) patients gave a history of bleeding or were admitted during an episode of hemorrhage. Of these 450 patients, requiring hospitalization or with a history of bleeding, 163 (23.3 per cent) were admitted to our hospital during or immediately after their first hemorrhage. Of the others 287 (41 per cent) had had 2 or more episodes of bleeding (Table IV).

TABLE III. AGE INCIDENCE AND DEGREE OF BLEEDING

AGE	NO. OF PATIENTS	TYPE BLEEDING		
		MASSIVE	MODERATE	MINIMAL
20-29	51	17	5	29
30-39	99	26	26	47
40-49	76	27	28	21
50-59	150	69	30	51
60-69	72	34	24	14
70-79	2	2	0	0
Totals	450	175 (25% of 700)	113 (16% of 700)	162 (23% of 700)

In 121 (17.3 per cent) of the patients with bleeding, hemorrhage had occurred more than 3 times before they were referred for definitive surgical intervention.

A partial gastrectomy was performed as an emergency procedure in 81 (19 per cent) of the patients admitted with bleeding or a history of repeated

TABLE IV. AGE INCIDENCE AND RECURRENT HEMORRHAGE

AGE	NO. OF TIMES HEMORRHAGE OCCURRED				
	INITIAL	TWO	THREE	OVER THREE	TOTAL
20-29	10	10	9	10	39
30-39	26	10	20	25	81
40-49	17	19	23	23	82
50-59	72	32	17	35	156
60-69	37	21	5	15	78
70-79	1	0	0	11	12
80-89	0	0	0	2	2
Totals	163 (23.3%)	92 (13.1%)	74 (10.6%)	121 (17.3%)	450 (64.3%)

hemorrhage, while in 101 (24 per cent) operations were performed 7 to 14 days after massive or moderate hemorrhage. In the remainder the operation performed was an elective procedure.

METHODS

Preoperative Gastric Analyses.—Preoperative gastric analyses for free acids in the fasting stomach and after histamine injection were performed in almost all cases except in patients with active hemorrhage or those with marked pyloric obstruction. In 60 per cent of the cases, free hydrochloric acid was present in the fasting stomach in amounts higher than 35 U. After histamine injection 82 per cent of the patients showed free acids over 35 U. (Table V).

TABLE V. PREOPERATIVE GASTRIC ANALYSES

NO. OF CASES	FASTING (U.)	NO. OF CASES	AFTER HISTAMINE (U.)
219 (40.5%)	1-35	99 (18.5%)	1-35
161 (29.8%)	36-50	165 (30.8%)	36-50
161 (29.8%)	Over 51	271 (50.7%)	Over 51
541 (77.3%)		535 (76.4%)	

Type of Operation Performed.—A partial gastrectomy was performed through a supraumbilical, transverse, transrectus, elliptical, abdominal incision which was closed by suturing the anterior and posterior rectus sheaths with interrupted silk sutures. Approximately 75 per cent of the stomach was resected, including practically all of the lesser curvature. In all cases except 2, the duodenal ulcer with associated fibrosis was removed. An anterior gastrojejunal anastomosis was performed. In those patients in whom the stomach was large and the gastric ostium was wide, the lesser curvature portion of the stomach ostium was closed, allowing for a modified Hofmeister type of anastomosis. The afferent loop was short in the majority of cases, averaging 4 to 5 inches in length. The majority of the patients were ambulated on the first postoperative day.

RESULTS

The follow-up studies were conducted at 6 month intervals for the first few years, at yearly intervals for the succeeding 2 years, and every 3 to 4 years

thereafter. At the yearly and later follow-up periods the patients were admitted to the hospital for a complete clinical and laboratory evaluation.

Of the 700 patients operated upon, 602 (86 per cent) were adequately followed. The longest follow-up was 12 years and the shortest 18 months. Sixty-two per cent of this group were followed over 3 years and 24 per cent were followed 5 years or longer.

Associated Surgical Procedures.—Other operative procedures performed in conjunction with partial gastrectomy totaled 153 (22 per cent). These were required in many to remove or correct other associated pathologic conditions (Table VI).

TABLE VI. ASSOCIATED SURGICAL PROCEDURES

OPERATION	CASES
Appendectomy	21
Cholecystectomy	17
Cholecystojejunostomy	12
Cholecystostomy and choledochotomy	6
Diverticulum, duodenal, excision of	2
Diverticulum, jejunal, excision of	1
Diverticulum, Meckel's, excision of	1
Gastroenterostomy, resection of	43
Gastrotomy	14
Hernioplasty, ventral	11
Liver, cyst, excision of	1
Miscellaneous	9
Pancreatic cyst, excision of	2
Resection, carcinoma, transverse colon	1
Splenectomy	12
Total	153 (21.85%)

Postoperative Complications.—There was a total of 427 (61 per cent) postoperative complications in 301 patients (43 per cent). The most frequent complications were pulmonary, occurring in 102 (24 per cent) patients. Vascular complications occurred in 77 (18 per cent) and wound complications in 55 (13 per cent). Table VII lists all of the complications.

There were 6 (0.86 per cent) wound dehiscences, and 12 (1.72 per cent) postoperative incisional hernias.

Postoperative Deaths.—There were 28 (4 per cent) deaths in the entire series of 700 patients. This included the 175 patients who were operated upon during or shortly after an episode of massive hemorrhage. In this latter group there were 16 deaths, a mortality rate of 9.1 per cent.

Excluding the 175 patients who were operated upon for massive hemorrhage from the over-all mortality rate of 4 per cent, there were 12 deaths in 525 patients, *a mortality rate of 2.28 per cent* (Table VIII).

Several of the deaths which occurred in the 175 patients operated upon for massive hemorrhage were similar to those that occurred in the group with elective operations (Table IX).

Postoperative Gastric Analyses.—These studies revealed no free acid in the fasting specimen in 509 (85 per cent) cases and no free acid after histamine

in 369 (62 per cent). In 93 cases the fasting gastric specimen contained 1 to 50 U. and after histamine 229 showed 1 to 75 U. of free acid (Table X). In other words, 85 per cent of the 602 patients studied were achlorhydric in the

TABLE VII. POSTOPERATIVE COMPLICATIONS

TYPE		NO.	%
Wound			
Dehiscence		6	0.85
Hematoma		26	3.7
Hernia, postoperative		13	1.8
Infection		10	1.4
	Total	55	7.8
Pulmonary			
Atelectasis		64	9.1
Embolism		3	0.4
Infarction		13	1.8
Pneumonia		8	1.1
Pneumonitis		14	2.0
	Total	102	14.4
Vascular			
Phlebothrombosis		7	1.0
Thrombophlebitis		25	3.5
Postoperative hemorrhage			
Gastrointestinal tract		28	4.0
Other		17	2.4
	Total	77	10.9
Miscellaneous			
Abscess, subhepatic		7	1.0
Cerebral hemorrhage		4	0.57
Cholecystitis, acute		6	0.85
Diarrhea, nonspecific		22	3.1
Diarrhea, enterocolitis, specific		6	0.85
Diverticulitis, acute		9	1.3
Ileus, paralytic		5	0.7
Jaundice, homologous serum		26	3.7
Jaundice, obstructive		9	1.3
Jaundice, transient		7	1.0
Leak, duodenal stump		22	3.1
Myocardial infarction		7	1.0
Obstruction, efferent loop (transient)		21	3.0
Oliguria or anuria		5	0.7
Pancreatitis, acute		4	0.57
Pancreatitis, necrotizing		6	0.85
Retention, gastric		17	2.4
Uremia		5	0.7
Urinary tract infection		5	0.7
	Total	193	27.39
Grand Total		427	60.5

TABLE VIII. MORTALITY RATE IN 525 ELECTIVE OPERATIONS

NO.	CAUSE	AGE OF PATIENT
1	Acute coronary thrombosis	60
5	Acute necrotizing pancreatitis	31, 32, 41, 48, 52
1	Hepatic failure	64
3	Infaret, pulmonary	28, 36, 51
1	Massive cerebral hemorrhage	64
1	Obstruction, common duct	31
Total 12 (2.28%)	Average age	44.6 years

TABLE IX. MORTALITY RATE IN 175 MASSIVE HEMORRHAGE CASES

NO.	CAUSE	AGE OF PATIENT
1	Acute coronary occlusion	60
1	Anastomotic breakdown	58
2	Gangrene of duodenum	57, 61
4	Hemorrhage, gastric postoperative	39, 55, 58, 61
1	Hemorrhage, hepatic artery	53
4	Infarction, myocardial	26, 49, 51, 60
3	Perforation, duodenal stump	31, 56, 67
Total 16 (9.1%)	Average age	52.6 years

TABLE X. POSTOPERATIVE GASTRIC ANALYSES

NO. OF CASES	FASTING (U.)	NO. OF CASES	AFTER HISTAMINE (U.)
509 (85%)	0	369 (62%)	0
53 (9%)	1-35	181 (30%)	1-35
40 (6%)	36-50	30 (5%)	36-50
0	Over 50	18 (3%)	Over 50
Totals 602		598	

fasting specimen and of this number 62 per cent remained achlorhydric after histamine injection.

Evaluation of Follow-up Studies.—After operation 33 per cent of the patients gained weight, whereas 40 per cent lost weight, and the remaining 27 per cent showed no change. The dumping syndrome occurred in 22 per cent of the patients and in 15 per cent it was mild and easily controlled by dietary measures. Diarrhea was troublesome in 12 per cent. Eighty per cent of the patients were on a regular diet of 3 meals a day. Eighty-three per cent were free from abdominal pain and their ulcer syndrome was relieved.

The over-all evaluation of the results in 602 (86 per cent) patients on whom adequate follow-ups were obtained was considered excellent to good in 83 per cent.

COMMENT

Partial gastrectomy in the treatment of chronic duodenal ulcer continues to be a good procedure which causes reasonably low mortality and morbidity rates, with a low incidence of undesirable postoperative sequelae. The mortality rate of 2.28 per cent in elective patients is considered low in view of the fact that in 698 cases the ulcer was removed and that in over 50 per cent of the patients the operation was performed by the senior house officers. In the former instance, the resection of the ulcer poses many complex problems and in itself leads to increased morbidity and mortality rates. It is our policy now to leave the ulcer in situ except in patients who are bleeding or in patients in whom the ulcer is so situated as to preclude a safe and adequate duodenal closure.

The mortality rate of 9.1 per cent in the group of 175 patients who had emergency operations during hemorrhage is considered low since many of these patients presented poor risks because of repeated episodes of bleeding and

TABLE XI. RESULTS OF FOLLOW-UP STUDIES*

	NO. OF CASES	PERCENTAGE
Weight		
Gain	196	32.5
Loss	240	39.9
No change	166	27.6
Appetite		
Excellent to good	472	78.4
Fair to poor	130	21.6
Diet		
Regular	481	79.9
Restricted	121	20.1
Marked restriction	17	14.0
Mild restriction	104	86.0
Frequency of Feedings		
Three times daily	289	48.0
Three to 5 times daily	242	40.2
More than 5 times daily	71	11.8
Bowel Habits		
Normal	438	72.7
Constipation	91	15.1
Diarrhea	52	8.6
Varying (diarrhea-constipation)	21	3.5
Dumping Syndrome		
None	466	77.4
Mild	88	14.6
Moderate	27	4.5
Severe	21	3.5
Abdominal Pain		
"Ulcer-like" pain	19	3.1
Distress due to overindulgence	81	13.5
No unusual or unexplained pain	502	83.4
Ability to Work		
Good	401	66.6
Fair	88	14.6
Poor	59	9.8
Unable to work (other disease, retired, etc.)	54	9.0

*A marginal or stomal ulcer developed in only 3 patients, an incidence of 0.4 per cent.

recurrent shock. By a more cooperative alliance of the medical and surgical groups as a team in managing patients with a bleeding ulcer, we can expect a progressive decline in the mortality rate. If operation is instituted at the proper time and performed by an experienced surgical team, lower morbidity and mortality rates can be expected. Clinical judgment and experience in such cases usually result in a lowering of the mortality rate. It is important to recognize that the young patient with a bleeding ulcer can bleed as rapidly and as often as a patient beyond 50 years of age and that death can occur in these younger patients almost as frequently as in the older ones. The major difference lies in the ability of the younger person to withstand repeated episodes of shock.

The fact that marginal ulcer has occurred in only 0.4 per cent of the patients in this series speaks highly for the procedure in that the extent of resection was sufficiently high to result in persistent achlorhydria in 85 per

cent of the patients. However, a 75 per cent resection also has its shortcomings. These include failure to gain weight because of small gastric reservoir in over 39 per cent of the patients, dumping syndrome, bowel disturbances, frequent daily feedings to maintain strength and weight, and occasionally gastric disturbances when patient overindulges in food intake.

When we consider the over-all favorable results of this procedure and its primary ability to relieve these patients of their ulcer syndrome and prevent further complications, we can place this operation near the top of the list of surgical procedures currently being performed in the treatment of chronic duodenal ulcer.

SUMMARY AND CONCLUSIONS

Partial gastrectomy with a short afferent jejunal antecolic gastrojejunostomy continues to be a very good procedure for the treatment of chronic duodenal ulcer. In 83 per cent of the 700 patients treated in this series the results were considered good to excellent.

The mortality rate of 2.2 per cent in elective operations and an over-all mortality rate of 4 per cent (including 175 patients operated upon during massive hemorrhage) is low and within an acceptable range.

A low incidence of marginal ulcer, 0.4 per cent, indicates that an adequate resection was performed.

The extent of resection is responsible for some of the undesirable sequelae, such as failure to gain weight or loss of weight in 68 per cent of the patients, dumping syndrome in 22 per cent, frequent daily feedings in 52 per cent, and bowel disturbances in 12 per cent.

Partial gastrectomy as described in this series remains as our second choice of currently proposed surgical procedures for treatment of chronic duodenal ulcer. Our first choice is antrectomy with bilateral vagectomy.

WEIGHT LOSS AFTER GASTRECTOMY: COMPARATIVE IMPORTANCE OF RESIDUAL POUCH CAPACITY, PRESENCE OF AN INNERVATED PYLORUS, FAT EXCRETION, AND POSTOPERATIVE SYMPTOMS

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GASTRIC surgery for peptic ulcer has progressed to the point where mortality rates and recurrence rates are low enough to cause little concern to those physicians who must decide whether or not to recommend resection as therapy. However, the morbidity rate after partial gastrectomy is a significant variable to be taken into account, and has led to extensive studies of different types of gastrectomy and continuing attempts to perfect new variants which will minimize disability. One of the operations thought to be most promising is the innervated segmental resection in which the pylorus is retained.

The surgical literature is replete with animal experiments and surveys of operations in human beings which claim the advantages of one procedure over others in common use. The most popular operation at this time is the Billroth II resection because it has led to the fewest recurrences. However, reports have accumulated which suggest that morbidity after this operation (the persistence of symptoms and the inability of the patient to gain weight) is greater than with other current procedures. Many have implied, following the lead of Everson,[3, 4] that the nutritional impairment is largely due to abnormal fat loss in the stool. Some data have been published[8] which cast doubt upon this conclusion, but the idea still prevails. Among the new procedures, the segmental resections in which the pylorus is retained have received particular attention, and the impression has already been seeded that these operations result in fewer postoperative symptoms and less nutritional impairment.

The initial objective of the present study was a comparison of postoperative symptoms, weight loss, and lipid (total fat, fatty acids, and cholesterol) excretion among patients subjected to various types of gastric resection, including innervated segmental, Billroth II, Billroth I, and total resections. Since a decrease in food intake plays an obviously important part in weight loss after gastrectomy, an attempt was made to evaluate the role of the residual gastric reservoir in weight loss, using the weight of stomach removed at operation as an indirect, admittedly crude, measure of residual pouch capacity. In short, the

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relative importance of postoperative symptoms, the presence of an innervated pylorus, lipid loss, and the residual pouch capacity in predicting weight loss after gastrectomy are compared.

METHODS

Patients.—Over a 4-month period 40 patients who had undergone partial gastrectomies for complicated peptic ulcers were studied. Duodenal ulcer patients were subjected to Billroth II or segmental resections. The allocation was random (even-odd alternation) in most instances. In each case at least 75 per cent of the stomach was removed. The amount of tissue resected was weighed soon after removal. In the innervated segmental resection performed in alternate patients, approximately 5 cm. of the antrum and 7 cm. of the fundus were retained and the vagus fibers to the antrum and pylorus were intact. The operation was devised and has now been evaluated by Ferguson.[5] Gastric ulcer patients underwent a 75 per cent resection and a Billroth I reconstruction. These patients were first studied within 1 to 3 weeks of gastrectomy and followed at 3-month intervals. Two patients were excluded from the analysis because they could not cooperate. One was mentally confused and the other psychotic.

In addition to the 38 partial gastrectomy patients, 7 patients with total or near-total (Billroth II) resections for suspected cancer who returned for follow-up during this interval, and 4 patients hospitalized with a dumping syndrome were studied similarly. For the fecal studies, 19 convalescent patients, recovering from minor illnesses and free of gastrointestinal disease, formed a control group. There were thus 4 gastrectomy subgroups—Billroth I, Billroth II, segmental, and total, in addition to the controls and patients with dumping syndrome for comparison.

Prior to the fecal studies, all patients were placed on a 2,000 calorie diet supplying 100 Gm. fat, 185 Gm. carbohydrate, and 85 Gm. protein. The food was subdivided into 6 feedings and intake carefully recorded. The calculated content of the diet was verified twice by chemical analyses.

Symptoms such as epigastric pain, nausea, cramps, sweating, diarrhea, palpitation, fullness, and weakness were noted and rated as to frequency and severity during the 5 or 6 day periods that fecal collections were being made. The over-all symptom rating was mild when only very mild sporadic individual symptoms occurred, moderate when several symptoms occurred daily, and severe when daily symptoms occurred which at least interfered with eating temporarily. Similar ratings of the patient's symptoms while at home during the postgastrectomy follow-up period were made after careful questioning.

Each patient was weighed preoperatively, postoperatively, and at each recall visit. The patient's usual preoperative weight was obtained from previous hospital records in all but 2 instances.

Fecal Studies.—Complete stool collections were made over a 5 or 6 day period while intake was recorded. The stools collected over the last 3 days of this period were pooled, homogenized, and analyzed in duplicate for total fat, fatty acids, cholesterol, nitrogen, and dry weight by standard methods.[6] Results are expressed in grams per day. No correction was made for decreased fat

intake in 9 patients who failed to eat the entire meal, since we believe that in this range of fat intake there is little relationship between intake and excretion. No patient ate less than one-half the total calories provided. The balance studies were first performed 1 to 3 weeks after gastrectomy and were repeated in 24 patients from 4 to 43 months later.

Validity of Fat Excretion Calculations.—Most studies reporting fat excretion data have expressed lipid excreted as a percentage of the lipid ingested. In this procedure it is assumed that the amount of fat excreted is proportional to the amount ingested. Wollaeger and co-workers[10] have assembled data in the normal range suggesting that this assumption is roughly correct when the fat intake is varied from 30 to 350 Gm. per day, and it is apparently on the basis of their conclusions that the prevailing practice rests. This conclusion, however, is apparently not generally applicable in the range of the usual fat intake. Annegers, Boutwell, and Ivy[1] found that varying fat intake in 40 normal medical students from 60 to 120 to 150 Gm. per day did not alter the excretion of fat significantly. We have assembled data bearing on this point from reports listing values observed in individual postgastrectomy patients (Table I). As

TABLE I. EFFECT OF DOUBLING FAT INTAKE ON FAT EXCRETION IN GASTRECTOMY PATIENTS

SOURCE OF DATA	TYPE OF RESECTION	FECAL FAT EXCRETION			
		ABSOLUTE (GM.)		%	
		50 GM. INTAKE	100 GM. INTAKE	50 GM. INTAKE	100 GM. INTAKE
Rekers and associates[9]	Total	12	13	24	13
	Total*	11	12	16	10
Brain and Stammers[2]	Total	17	28	34	28
	Total	12	8	24	8
	Total	20	18	40	18
	Partial	12	25	24	25
	Partial	18	20	36	20
	Total	10	10	20	10
	Total	18	17	36	17
	Partial	20	19	40	19
	Partial	13	12	26	12
Jones and associates[7]	Partial†	6	13	6	7
Present authors	Total‡	19	23	19	12
Average		14	17	27	15
Average difference		+3		-12	

*70 and 125 Gm. fat intake.
†98 and 183 Gm. fat intake.
‡100 and 185 Gm. fat intake.

can be seen from the table, with 2 exceptions, an increase in fat intake from 50 to 100 Gm. did not result in a significant increase in fat excreted. The average difference in grams of fat excreted for all patients, including 3 who received more than 100 Gm. of fat, was +3, whereas the average difference in percentage fat excreted was –12. It is evident that, as a rule, doubling the amount of fat ingested within this range, even in the presence of abnormal fat excretion, more than doubles the fat absorbed rather than altering the amount of fat excreted. Percentage excretion, instead of remaining constant for a given individual as generally assumed, varies inversely with intake. It can be seen readily that it is simplest and most accurate to present lipid excretion data in absolute terms.

Furthermore, as much fat as can be given without discomfort, irrespective of fecal fat values, should be included in the diet of such patients as a means of building up caloric intake.

RESULTS

Descriptive Data.—The average age of all gastrectomy patients was 49 years, with a range of 27 to 68 years. There were no essential differences among the subgroups (Table II). By selection, all patients with segmental and 8 of 12 with Billroth II resections had a duodenal ulcer, whereas 1 of 8 patients with Billroth I resections had a duodenal ulcer. The reasons for operation were essentially similar among the ulcer patients. The incidence of preoperative complications was similar among the subgroups. An average of 205 Gm. of stomach tissue was removed from the partial gastrectomy patients. There was little difference between the segmental and Billroth II cases, but somewhat less tissue was removed with the Billroth I operation (Table II).

The usual preoperative weights (Table III) were, on the average, the same as the ideal weights calculated from standard tables, though the former were more variable, as might be expected. Body weight on the day of operation was an average of 7 per cent below preoperative weight for partial gastrectomy and 15 per cent for total gastrectomy patients. The maximal weight loss was noted at 3 months, the average being 13 per cent for partial and 20 per cent for total gastrectomy patients. Thereafter a slow weight gain was noted, and at 1 year partial gastrectomy patients were about 10 per cent below preoperative weight. No differences among subgroups were noted, and wide variation in weight loss among individuals was typical.

Significant symptoms were observed in one-third of partial gastrectomy patients during the first 3 weeks after operation. After several months this incidence had dropped to 3 per cent (Table IV). No relationship was observed between the occurrence of symptoms and age, weight loss, weight of tissue removed, or lipid excreted (Table V).

Initial fat excretion studies were made during the second and third weeks after gastrectomy (Table VI). The average time interval was 13 days. Follow-up observations were made over a variable period ranging from 1 to 72 months after operation. Typically the follow-up measurements were made within 1 to 1½ years in the case of partial gastrectomy patients and within 2 years in the case of total gastrectomy patients. Immediately after operation those with partial gastrectomies excreted an average of more than twice as much lipid as the controls. One-half excreted more than 10 Gm. per day and one-fifth more than 20 Gm. per day. At follow-up examination, however, none excreted 20 Gm. per day and only one-third excreted more than 10 Gm. per day. Only occasionally was the abnormality more than mild. Those partial gastrectomy patients with initially abnormal lipid excretion were later found on repeat study to have cut their lipid loss in half (Table VII). Those normal initially were unchanged on repeat study. Fatty acid excretion followed the pattern of total lipid excretion almost exactly. Cholesterol excretion was always normal (Table VI).

TABLE II. AGE, PREOPERATIVE COMPLICATIONS, FINAL DIAGNOSES, AND WEIGHT OF TISSUE REMOVED, BY SUBGROUP

SUBGROUP	NO.	AGE (YR.)		PREOPERATIVE COMPLICATIONS (%)						FINAL DIAGNOSIS (%)			TISSUE REMOVED (GM.)	
		MEAN	RANGE	OBSTRUCTION	BLEEDING	PERFORATION	OBP*	INTRACTABILITY	CARCINOMA	DUODENAL ULCER	GASTRIC ULCER	CARCINOMA	MEAN	RANGE
Control	19	45	21-68	—	—	—	—	—	—	—	—	—	—	—
Segmental	18	44	27-68	22	44	22	67	78	0	100	0	0	206	94-358
Billroth II	12	54	37-64	8	42	25	67	33	17	67	17	17	230	125-350
Billroth I	8	54	37-68	14	57	0	57	14	29	14	86	0	167	139-207
All partial gastrectomy	38	49	27-68	16	46	19	65	51	11	73	22	5	205	94-358
Total	7	50	34-68	0	0	0	0	0	100	0	29	71	—	—
All gastrectomy	45	49	27-68	14	40	17	57	45	21	61	23	16	—	—
Dumping syndrome	4	44	27-59	0	50	25	50	100	0	100	0	0	199	190-213

*OBP, obstruction, bleeding, or perforation.

TABLE III. POSTOPERATIVE WEIGHT CHANGES, BY SUBGROUP

SUBGROUP	NO.	IDEAL WEIGHT (LB.)		USUAL PREOPERATIVE WEIGHT (LB.)		DAY OF OPERATION (% OF PREOPERATIVE)		3 MO. POSTOPERATIVE (% OF PREOPERATIVE)		6 MO. POSTOPERATIVE (% OF PREOPERATIVE)		1 YR. POSTOPERATIVE (% OF PREOPERATIVE)	
		MEAN	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE
Control	19	166	145-191	—	—	—	—	—	—	—	—	—	—
Segmental	18	167	149-184	169	140-210	94	85-100	88	78-101	89	83-97	90	81-101
Billroth II	12	165	145-186	164	142-217	91	83-100	86	74-97	86	70-95	88	77-90
Billroth I	8	159	149-163	143	115-160	94	84-102	87	73-100	89	73-100	91	82-101
All partial gastrectomy	38	165	145-186	162	115-217	93	83-102	87	73-101	88	70-101	89	77-101
Total	7	166	153-178	157	132-200	85	77-95	80	74-86	84	75-88	83	75-88
All gastrectomy	45	165	145-186	161	115-217	92	77-102	86	73-101	87	70-101	88	75-101
Dumping syndrome	4	156	139-169	153	130-175	93	80-98	81	67-93	84	77-94	85	77-91

TABLE IV. PERCENTAGE OF PATIENTS WITH MODERATE OR SEVERE SYMPTOMS AT INITIAL AND FOLLOW-UP POSTOPERATIVE EVALUATION, BY SUBGROUP

SUBGROUP	INITIAL (%)	FOLLOW-UP (%)
Segmental	38	0
Billroth II	50	0
Billroth I	0	13*
All partial gastrectomy	34	3
Total	—	0
All gastrectomy	—	2
Dumping syndrome	—	25†

*One of 8 patients.
†One of 4 patients.

TABLE V. RELATIONSHIP OF SEVERITY OF SYMPTOMS TO AGE, WEIGHT LOSS, AND LIPID EXCRETION AMONG PARTIAL GASTRECTOMY PATIENTS

VARIABLE	SYMPTOMS	NO.	MEAN	RANGE
Age (yr.)	Absent or mild	19	48	30-68
	Moderate or severe	12	52	27-67
Maximum weight loss (% of preoperative)	Absent or mild	23	15	5-30
	Moderate or severe	15	18	9-27
Weight of tissue (Gm.)	Absent or mild	22	201	94-358
	Moderate or severe	15	211	125-350
Fecal lipid (Gm.)	Absent or mild	19	14	6-30
	Moderate or severe	12	12	2-28

Nitrogen excretion was essentially normal, though in a few cases it reached abnormal levels. The dry weight of the stool was essentially similar to that of the controls, although 2 high values tended to raise the mean. No significant differences in any of these variables were found among the various types of gastrectomy, including the total gastrectomy.

Interrelationships.—Scatter diagrams relating fatty acid excretion, dry weight of stool, nitrogen excretion, and weight of stomach tissue resected to total lipid excretion are shown in Fig. 1, *A, B, C,* and *D*. Fatty acid excretion was practically perfectly correlated with total lipid excretion irrespective of subgroup ($r = 0.96$). The dry weight of the stool also was highly correlated with lipid excretion ($r = 0.80$), and for purposes of group studies adequately reflects fat excretion. Although there was relatively little variation in nitrogen excretion, a significant positive correlation ($r = 0.51$) with lipid excretion was evident. There was no significant association between lipid excretion and the amount of tissue resected ($r = 0.23$). The correlation between age and lipid excretion was 0.01.

Weight loss was not related to lipid excretion as shown in Fig. 2, *A*. The correlation coefficient was 0.12. In contrast, despite the fact that the weight of tissue removed is a very imperfect measure of residual stomach capacity, a significant correlation ($r = 0.45$) was noted between weight loss and the amount of tissue resected, under tissue weights of approximately 4 Gm. per kilogram of body weight (Fig. 2, *B*). Tissue weights falling above this figure were from patients with obstruction.

TABLE VI. INITIAL AND FOLLOW-UP FECAL EXCRETION MEASUREMENTS, BY SUBGROUP

SUBGROUP	NO.	TIME OF STUDIES		TOTAL LIPID (GM.)		CHOLESTEROL (GM.)		NITROGEN (GM.)		DRY WEIGHT (GM.)	
		MEAN	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE	MEAN	RANGE
A. Initial observations											
Control	19	—	—	5	2-8	0.55	0.13-1.11	1.1	0.5-1.6	25	10-39
Segmental	15	13 days	8-17	13	2-30	0.54	0.14-1.07	1.5	0.2-3.1	35	6-62
Billroth II	10	13	10-23	14	6-29	0.49	0.17-0.94	1.3	0.3-2.5	32	11-55
Billroth I	8	11	6-16	11	4-25	0.42	0.13-0.94	1.0	0.5-1.6	26	9-46
All partial gastrectomy	33	13	6-23	13	2-30	0.50	0.13-1.07	1.3	0.2-3.1	32	6-62
B. Follow-up observations											
Segmental	12	10 months	6-15	8	3-18	—	—	0.8	0.5-1.3	25	11-47
Billroth II	7	16	6-36	11	5-17	—	—	1.5	0.6-3.4	40	22-51
Billroth I	5	18	4-43	10	3-19	—	—	1.2	0.7-1.5	31	13-53
All partial gastrectomy	24	13	4-43	9	3-19	—	—	1.1	0.5-3.4	27	11-53
Total	7	24	1-72	11	7-19	—	—	1.1	0.6-1.8	26	16-38
All gastrectomy	31	15	1-72	10	3-19	—	—	1.1	0.5-3.4	27	11-53
Dumping syndrome	4	19	3-60	12	9-14	—	—	1.8	1.1-2.6	41	25-58

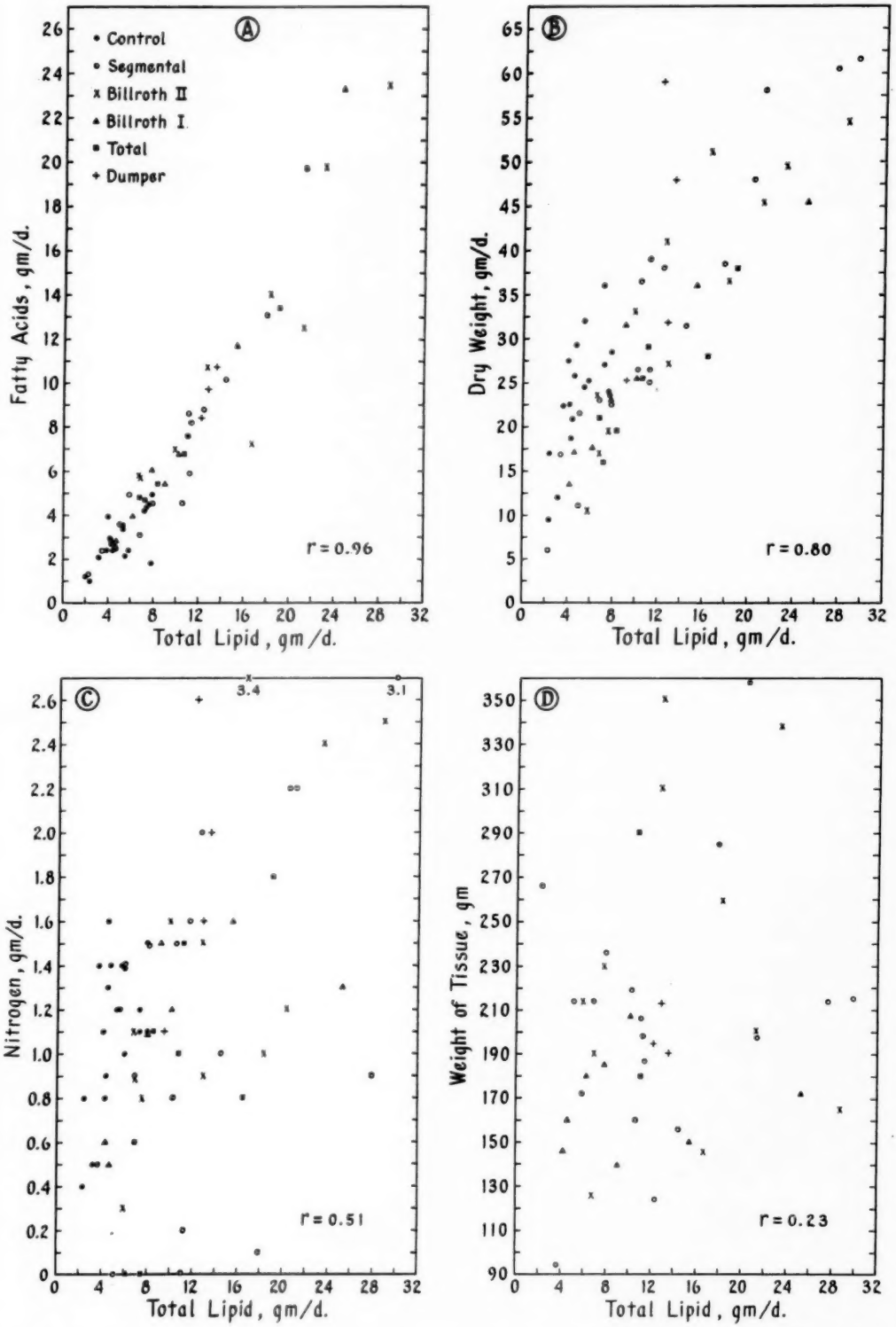

Fig. 1.—Relationships between total lipid excretion and fatty acid excretion, dry weight of stool nitrogen excretion, and weight of tissue resected.

Maximum Post-op. Weight Loss, % of Pre-op.
Minimum Post-op. Weight, % of Pre-op.
Total Lipid, gm/d.
r = 0.12
Maximum Post-op. Weight Loss, % of Pre-op.
Minimum Post-op. Weight, % of Pre-op.
Weight of Tissue, gm/kilo
r = -0.45

Fig. 1.—Relationship of postoperative weight loss to lipid excretion and amount of tissue resected. Symbols are the same as in Fig. 1, *A*.

TABLE VII. RELATIONSHIP OF LIPID EXCRETION AT FOLLOW-UP TO NORMALITY OR ABNORMALITY OF INITIAL OBSERVATIONS AMONG PARTIAL GASTRECTOMY PATIENTS

	TOTAL LIPID EXCRETION (GM.)					
	INITIAL			FOLLOW-UP		
	NO.	MEAN	RANGE	NO.	MEAN	RANGE
Initial normal	6	7	5-8	6	6	3-12
Initial abnormal	10	18	11-29	10	9	3-19
Both	16	14	5-29	16	8	3-19

COMMENTS

These observations suggest that the critical determinant of postoperative nutritional state is the residual stomach capacity. The symptoms commonly occurring shortly after gastrectomy were not significantly associated with weight loss. In the majority of the patients they subsided rapidly, and after several months only a small proportion still had symptoms that interfered appreciably with their well-being.

Weight loss was also not significantly associated with fecal fat loss. The latter was, in fact, not a particular problem to the patients. At follow-up, at least 4 months after operation, only one-third of the partial gastrecomy patients, irrespective of type of procedure, excreted over 10 Gm. of fat per day and none excreted more than 20 Gm. These results support those of MacLean and coworkers.[8]

Retention of an innervated pylorus, as in the segmental resection, did not alter the pattern of weight loss or of fat excretion seen after Billroth II resections. In general, weight loss in the partial gastrectomy patients was unrelated to the type of procedure performed. The only variable significantly correlated with weight loss was the amount of stomach removed. The important factor is the postoperative food capacity of the stomach. Ideally, we are interested in the relationship between the postoperative stomach capacity and weight loss. The best indirect measure of residual capacity that we recorded was the weight of stomach tissue removed at operation. This is clearly a rather poor index of residual stomach capacity because factors such as hypertrophy of tissue at the time of resection, stretching or contraction of the residual pouch after the postoperative adjustment phase, and individual differences in stomach size, among others, are not taken into account. Even if the true correlation between weight loss and residual stomach capacity were perfect, the presence of all these extraneous factors operates to lower the observed correlation greatly when the indirect measure, weight of tissue removed at operation, is used as a reflector of residual capacity. The fact that a correlation of this magnitude (0.45) was detected at all is thus medically significant, since it is indicative of a much higher relationship between postoperative residual stomach capacity and weight loss.

We have evidence, then, of a significant relationship between body weight loss and postoperative pouch capacity, irrespective of the type of surgical procedure, while at the same time finding no relationship between weight loss and fat excretion. These data are direct evidence of the importance of residual pouch

capacity in maintaining nutrition, and of the comparative unimportance of fat excretion. It appears, as many have suspected for a long time, that more than 25 per cent of the stomach must be retained if nutrition is not to be compromised. Retention of the pylorus, as in the segmental resection, does not compensate for an inadequate residual stomach capacity.

We might presume that the reason gastrectomy patients cannot gain weight is that they eat little for lack of space in which to put food without discomfort. This is probably an oversimplified explanation in which the importance of appetite and hunger in determining food intake is ignored. What the effect of resection is on the physiologic bases of appetite, independent of other factors that are present, remains to be properly explored.

SUMMARY

1. Weight loss, postoperative symptoms associated with eating, and fecal lipid (total, fatty acids, and cholesterol) and nitrogen excretion were measured in 19 control and 45 postgastrectomy patients with Billroth I, Billroth II, innervated segmental, or total resections.

2. Preoperative and ideal weights were essentially comparable. Maximal weight loss was noted at 3 months, the average for partial gastrectomy patients being 13 per cent of the preoperative weight and for totals 20 per cent. At 1 year, partial gastrectomy patients averaged approximately 10 per cent below ideal weight. Wide variation among individuals was typical, and there were no significant differences among the types of gastrectomy.

3. Moderate or severe symptoms after meals occurred in one-third of patients 3 weeks postoperatively, but in only 3 per cent 1 year later. No relationship was observed between the occurrence of symptoms and type of gastrectomy, amount of stomach resected, age, or lipid excreted.

4. Within 3 weeks of operation total lipid excretion was normal in one-half of the gastrectomy patients, and only one-fifth excreted more than 20 Gm. per day. At follow-up after 4 or more months, lipid excretion was normal in two-thirds and none excreted 20 Gm. per day. Fatty acid excretion followed the pattern of total lipid excretion almost exactly. Cholesterol excretion was always normal. Nitrogen excretion was also generally normal and only an occasional patient showed a slight abnormality. No significant differences in any of these variables were found among the various types of gastrectomy patients, including those with total gastrectomy.

5. Loss of body weight in these patients was unrelated to postoperative symptoms, fecal fat excretion, or type of procedure, but was correlated significantly with the amount of stomach removed at operation.

6. Retention of an innervated pylorus with the segmental resection did not alter the pattern of lipid excretion or weight loss seen after Billroth II resections. The residual stomach capacity was probably the critical determinant of postoperative nutritional state, irrespective of the presence or absence of the pylorus.

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MASSIVE BOWEL RESECTION IN A PATIENT WITH 75 PER CENT GASTRECTOMY

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A MORE aggressive attitude toward the management of small bowel infarction secondary to mesenteric thrombosis or embolism has brought an increase in the number of massive intestinal resections.[2, 3] Although many studies have been carried out concerning the deficits resulting from bowel resection, the amount of intestine which can be removed and still permit a reasonably normal existence is yet to be determined.

The following case report concerns a patient who had undergone 75 per cent gastrectomy and vagotomy prior to an extensive resection of bowel. Only 15 inches of jejunum and the descending colon remained.

CASE REPORT

Clinical History.—

Present illness: The patient, a 58-year-old man, was admitted to the University Hospital at 8:00 P.M. on Sept. 22, 1959, after 12 hours of dull, aching, constant and nonradiating midabdominal pain of gradual onset. There had been no vomiting, but 3 to 4 loose brown stools had been passed prior to admission.

Past history: In 1943, laparotomies had been performed for trauma to the rectum and for biopsy of a fatty mass in the head of the pancreas. In 1955, the patient had undergone a vagotomy and 75 per cent gastric resection with Billroth I anastomosis for benign gastric ulcer.

A limited small bowel resection had been carried out in 1956 for mesenteric artery thrombosis. In 1957 there had been 2 laparotomies for adhesive ileus. Between operations, the patient had been well and active.

Physical examination: The patient was well developed, mildly obese, and in moderate distress from abdominal pain. The blood pressure was 170/90 and pulse respirations and blood pressure were normal. Positive physical findings were limited to the abdomen, which had a rounded contour marked by numerous healed incisions. Generalized abdominal tenderness was most marked in the right midabdomen and lower quadrant. Some rebound tenderness was present, but no rigidity. No masses or organs were palpable. The bowel sounds were hypoactive with normal pitch and no rushes. The rectum was normal and the stool was guaiac negative.

Laboratory data: At time of admission, the hemoglobin concentration was 15.4 Gm. per cent, hematocrit 52 per cent, white blood count 22,500, serum amylase 753 units, and the blood sugar 99 mg. per cent. The urinalysis was normal. X-ray studies of the abdomen showed several moderately dilated loops of small bowel in the right lower abdominal quadrant with fluid levels.

Hospital Course.—Observation of the patient for 6 hours after admission confirmed the diagnosis of bowel infarction secondary to mesenteric thrombosis. The abdomen became

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more distended and more tender to palpation. The temperature rose to 100.6° F. and the white blood count to 30,000. The hemoglobin concentration despite hydration, increased to 16.5 Gm. per cent.

Laparotomy was undertaken through a long right paramedian incision. The entire small bowel, except the proximal 15 inches of the jejunum, was obviously infarcted, as was the right and mid transverse colon. Exploration showed the superior mesenteric artery to be filled with friable atherosclerotic material. An endarterectomy was performed and the smaller arterial radicals flushed with procaine and heparin. There was no observable change in the bowel color. Procaine was then injected about the base of the superior mesenteric artery and about the celiac plexus. This also had no effect. In view of the extensive gastric resection which had been carried out previously, and the extensive resection of the small bowel and colon which was about to be undertaken, little hope was held for the patient. He appeared destined for a miserable existence and an early death. After resection, an end-to-end anastomosis was constructed between the remaining 15 inches of jejunum and the transverse colon just proximal to the splenic flexure. Pathologic examination of the surgical specimen showed extensive hemorrhagic necrosis.

Postoperative Course.—The patient progressed quite well for the first 2 weeks. Liquids were tolerated by the fourth day and a postgastrectomy type of diet by the eighth day. Four to 5 light tan liquid stools were passed daily. The diet was supplemented with crude pancreatic extract, bile salts, vitamins, and calcium gluconate. The diet was gradually changed to one containing a ratio high in carbohydrate with moderate protein and low fat. With this diet, the stools became semiformed and averaged 3 per day. Over the next few days a febrile reaction developed in response to a right subdiaphragmatic abscess which required surgical drainage on Oct. 20, 1959. The convalescence from this procedure was uninterrupted and the patient was discharged on Nov. 4, 1959. During the hospital stay, the dietary intake had varied between 1,800 and 2,200 calories per day. By the time of discharge, the patient had lost 44 pounds and was 16 pounds below his ideal weight of 156.

A study of the patient was made prior to discharge. The gastric juice after histamine stimulation contained no free acid. Upper gastrointestinal x-ray studies were quite interesting. There was evidence of a 75 per cent gastrectomy with gastroduodenostomy and rapid evacuation of the gastric stump. The small bowel loop distal to the ligament of Treitz showed marked saccular dilatation and no peristalsis (Fig. 1). Considerable amounts of barium remained in this sac after 1½ hours. There was no narrowing at the anastomosis and barium passed freely into the distal colon, particularly when the patient was supine. Blood chemistry determinations showed only persistently low calcium (8.6 mg. per cent) and cholesterol (90 mg. per cent) levels. The alkaline phosphatase level was elevated (15.2 King-Armstrong units) and the albumin-globulin ratio was reversed (3.2 to 4 Gm. per cent) with a normal total protein level. The oral glucose tolerance curve was flat. The stool contained neutral fat and rare meat and vegetable fibers.

Clinic Follow-up.—When discharged, the patient was on a diet of 180 Gm. of carbohydrate, 75 Gm. of protein, and 100 Gm. of fat with vitamin, pancreatin, and bile salts supplements. He was instructed to ingest 10 drops of 0.1N HCl in water with meals. Within 3 weeks of discharge, the patient had gained 9 pounds and had improved considerably in vigor and sense of well-being. He was passing a stool about 2 hours after each meal. They were moderate in amount, light brown, and semiformed. Four months after discharge, the patient's weight had stabilized at 148 pounds and he was working every day in his usual occupation as a bartender.

DISCUSSION

The patient described has had the most extensive resection of the intestinal tract yet reported in the medical literature.

A review of other reported cases of massive intestinal resection shows that the compensatory mechanism of the digestive and absorptive processes becomes

increasingly efficient, if the patient is able to adapt at all.[1] There is typically an initial marked weight loss followed by rapid gain to a stable level somewhat below the preoperative weight. The stools become semiformed and usually are passed only after meals. High fat content in the diet is usually poorly tolerated. The reason for this is not entirely clear, but it is probably because of a decrease in absorptive surface area and a deficiency or inactivation of pancreatic enzymes. This deficiency may be due in part to the loss of secretin which is formed in the upper two-thirds of the small bowel. Another factor may be the loss of basic juices from the pancreas and small bowel, so that neutralization of gastric acid does not take place.[4] This was true in a report of a patient presented by Jackson. All but 6 to 7 inches of small bowel had been removed and the jejunal pH was 3.0 to 4.6.[5] This level inactivates pancreatic enzymes and prevents efficient fat and protein breakdown.

Fig. 1.—Note the dilated jejunal segment which did not empty for 1½ hours. Repeated studies showed no peristalsis in this sac.

The absence of free gastric acid in our patient is felt to be an important factor in his favorable postoperative course. If the acid production had been normal, the deficiency of alkaline pancreatic juice and succus entericus certainly would have left insufficient base to neutralize this acid. The low duodenal and jejunal pH would have inactivated the pancreatic enzymes which consequently would fail to split fats and proteins to a form suitable for absorption. Loss of vagal innervation may also be implicated in the formation of the large, paralyzed jejunal bag in which there is prolonged retention for absorption of nutritive substances.

Whether or not this series of events is actually occurring in our patient is being investigated in our laboratories. Removal of the acid factor may prove to be of real value in selected patients who have a low jejunal pH or acid stool and who fail to stabilize their weight and regain vigor after a massive intestinal resection.

SUMMARY

Massive intestinal resection in a patient with a previous 75 per cent gastrectomy and vagotomy is compatible with reasonably good health and vigor, as shown in the patient presented here. The possible beneficial effect of reduced gastric acid and loss of vagal innervation has been discussed. Further experimental work is indicated to clarify this possibility.

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FORMATION AND MAINTENANCE OF AN ISOLATED, VAGALLY INNERVATED GASTRIC POUCH IN THE MONKEY

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QUANTITATIVE gastric secretory studies in primates are essentially nonexistent. During the past 2 years we have developed methods for obtaining quantitative studies of uncontaminated secretions from isolated, vagally innervated, parietal cell pouches in monkeys. Recent reports in the literature concerning the "executive" monkey, by Brady[1] and Porter and associates,[3] have stressed psychologic aspects of the ulcer diathesis. Their findings indicate the need for a vagally innervated, separated, parietal cell gastric pouch to evaluate better the effect of psychic stress upon gastric secretion in the monkey. Our purpose in this report is to describe techniques for the formation and maintenance of isolated, vagally innervated parietal cell pouches in monkeys.

METHODS

Healthy Macaca monkeys of the "pigtail" variety weighing between 4 and 7 kilograms were used. The utilization of a specially designed retaining chair is essential (Fig. 1). The animals were placed in the holding chairs 4 to 10 days prior to the day of operation to allow adjustment to the restrictive environment. The standard diet consisted of monkey biscuits, oranges, apples, potatoes, and lettuce, in the form of 2 meals per day. Food was withheld for 24 hours prior to operation, but water was permitted up to 12 hours preoperatively.

Surgical Technique.—Intravenous barbituates were used for anesthesia, the dose averaging 35 mg. per kilogram of body weight. Monkeys vary in response to barbituates. Therefore approximately two-thirds of the calculated dose was given initially for observation of the response, and further small increments were added as needed. The skin was prepared in a standard manner and strict aseptic surgical techniques were utilized during all operative procedures.

An upper midline abdominal incision was used and gave adequate exposure. Initial attempts to form a vagally innervated pouch by the standard mucosal-septal techniques used in dogs were unsuccessful, and a new method was developed. This involved isolation of a segment of the gastric corpus with retention of the vagal fibers and blood vessels as they spread out from the lesser curvature above the incisura. The pattern of vagal fiber distribution

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determined by postmortem anatomic studies on the monkey is shown diagrammatically in Fig. 2. The lines of transection in relation to the vagal fibers and blood vessels are also indicated in Fig. 2.

The basic steps of this operative procedure are illustrated in Fig. 3. An area on the lesser curvature near its midpoint, possessing the most abundant

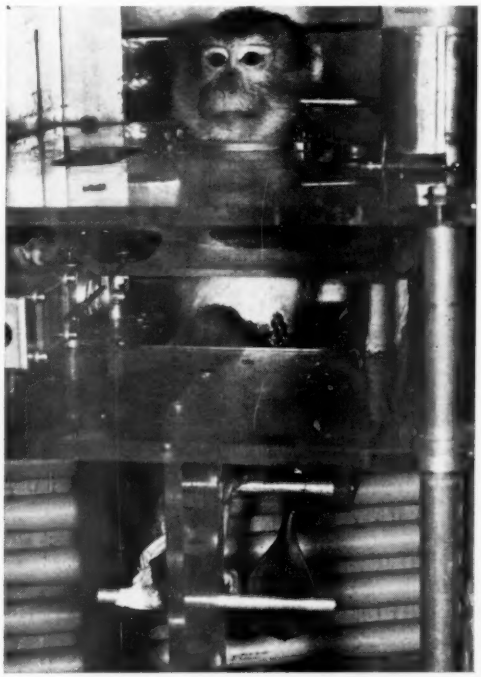

Fig. 1.—A monkey in the retaining chair. Pouch cannula with collecting tubing and bag are also shown.

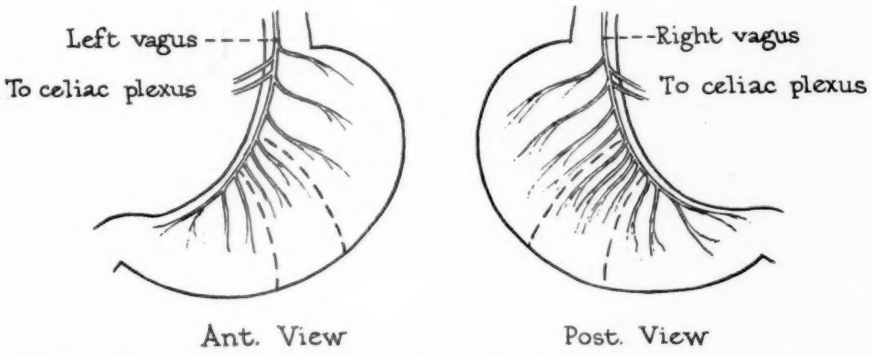

Fig. 2.—Diagram of the vagal fiber distribution to the stomach and the lines of transection of the corpus to form a vagally innervated, isolated pouch.

vessels and nerve fibers, was identified anteriorly and posteriorly. A small, curved, blunt hemostat was then used to lift the serosa with the vagal fibers and vessels off the lesser curvature (Fig. 3, *A*). Straight, narrow clamps were placed across the stomach as illustrated in Fig. 3, *B*. Care should be taken to avoid injury to the vagal fibers and blood vessels along the lesser curvature as they

spread out to supply the pouch and main stomach. Only 2 clamps were used and were both retained on the main stomach. The stomach was transected along each clamp and the open ends of the isolated segment then closed in 2 layers (an inner inverting continuous No. 4-0 chromic catgut layer and an outer layer of interrupted No. 4-0 silk). Before complete closure of the pouch, a small plastic cannula was inserted and brought out through a stab wound on the anterior wall of the pouch (Fig. 4). It is important to fix the cannula securely

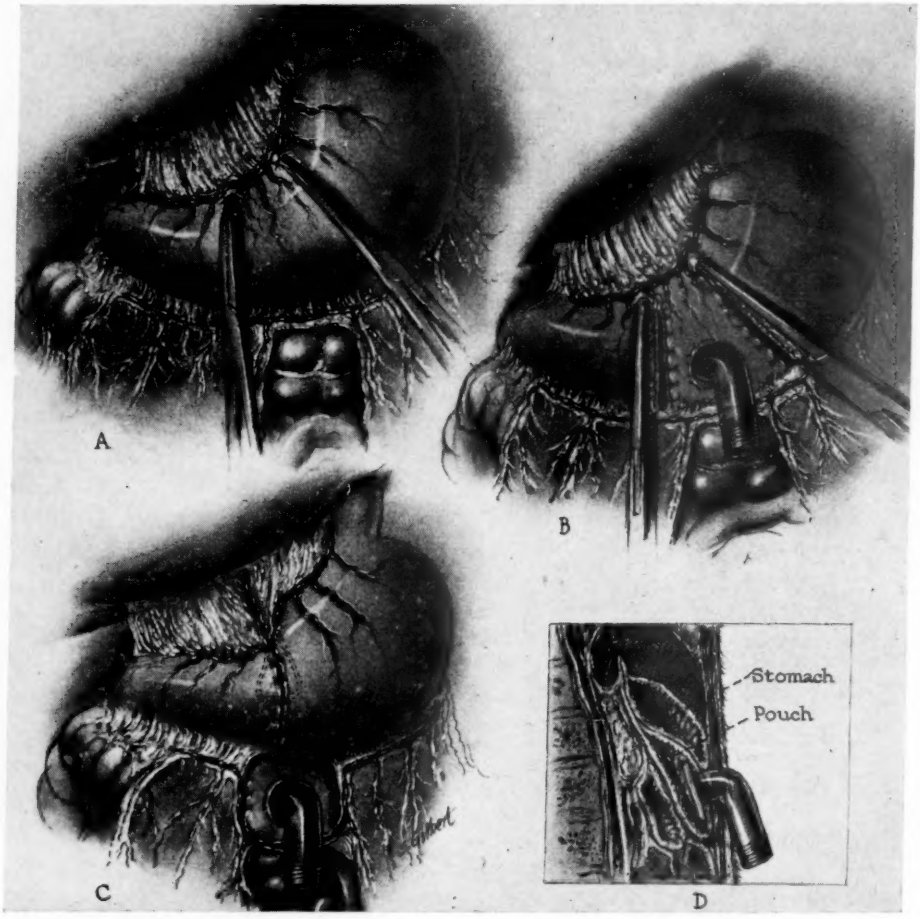

Fig. 3.—*A, B, C,* Basic steps in the technique of formation of a vagally innervated pouch in the monkey. *D,* Lateral view showing relationships of pouch, cannula, and main stomach.

in place with 2 layers of No. 4-0 silk in a purse-string fashion. Care should be taken to invert all the mucosa to prevent subsequent leakage of gastric juice and resultant erosion of surrounding tissue.

Gastrointestinal continuity was re-established by an end-to-end anastomosis of the stomach, with use of an inner continuous No. 4-0 chromic catgut layer and an outer layer of interrupted No. 4-0 silk. This anastomosis should be placed anteriorly to the isolated pouch to minimize any possible involvement of the more abundant posterior vagal fibers of the pouch in scar tissue along the

anastomosis. The posterior position of the pouch reduces the number of adhesions with the surrounding viscera, and will ease any future operations on the main stomach (Fig. 3, *C* and *D*).

The cannula was then brought out on the left, upper, anterior abdominal wall through a stab wound by means of the device described by DeVito and Harkins.[2] It is important to fasten the pouch securely to the anterior abdominal wall with 3 or 4 No. 4-0 silk sutures.

Postoperative Care.—The monkeys were kept for 24 hours postoperatively in a cage in a warm room. The ankles were taped together and the forearms fixed together behind the back to prevent the cannula from being pulled out.

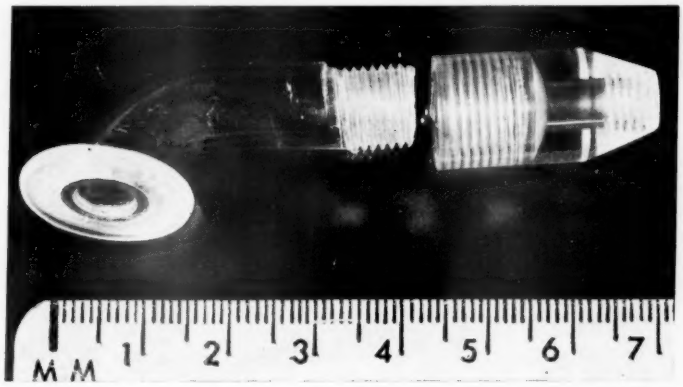

Fig. 4.—Plastic cannula and connecting endpiece used to collect pouch secretions.

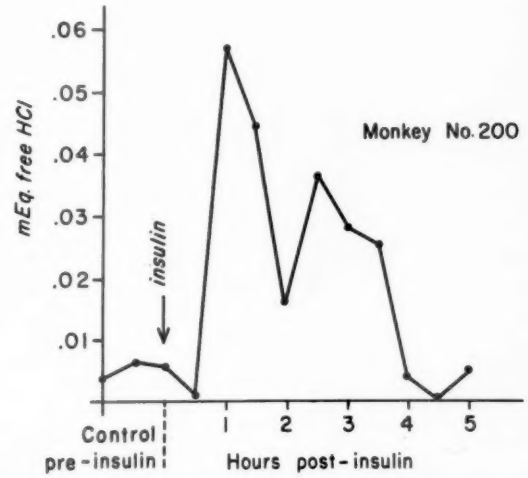

Fig. 5.—Effects of insulin hypoglycemia on free hydrochloric acid secretion of vagally innervated pouch.

The animals were able to move about without undue restriction. Attempts to place the animals in the retaining chairs before 24 hours will result in a high early postoperative mortality rate.

After 24 hours, the monkeys were placed in the chairs. Oral intake was restricted completely for 3 days or until a spontaneous bowel movement was

observed. During this initial period, fluid requirements were given by clysis. Antibiotics were not used routinely pre- or postoperatively.

Collection of Secretions.—Twenty-four hour collections of pouch secretions were begun 10 to 14 days postoperatively and were collected in a small rubber balloon attached to the cannula by a short plastic tube. Total 24-hour volumes for a 4 to 6 kilogram monkey on a standard diet with an innervated gastric pouch will average 40 to 75 c.c., or a total of about 5 to 10 mEq. of free hydrochloric acid.

Fig. 5 shows an insulin study on monkey No. 200, demonstrating a typical sharp early rise in secretion of free hydrochloric acid in the animal with a vagally innervated pouch. Also shown is an initial depression in secretion the first half hour followed by a "secondary" moderate rise starting about 2½ to 3 hours after insulin had been given. This phenomenon has been observed by Porter and associates[4] in the anesthetized monkey and by Shay and colleagues[5] in man. We are now investigating the factors involved in these findings.

SUMMARY

Satisfactory techniques for the construction and maintenance of isolated vagally innervated and vagally denervated parietal cell pouches in monkeys have been developed. The animals have been maintained for prolonged periods without deterioration. This is a practical investigational tool for the study of primate gastric secretory physiology which permits quantitative collection and measurement of uncontaminated gastric secretion in the unanesthetized but restrained monkey.

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THE EFFECT OF DIET ON GROWTH AND NITROGEN BALANCE AFTER INJURY

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DESPITE extensive investigation of protein metabolism in the postoperative patient in the 30 years since Cuthbertson's[5] initial observations, many practical issues remain unresolved. Of these, one of the most important to the clinician is the question of the efficacy of providing a high level of protein in the diet in the immediate postoperative or posttrauma period. There is controversy not only concerning the ability of the patient to utilize whole protein, amino acid mixtures, and hydrolysates given orally or parenterally, but also concerning the advisability of attempting to accelerate the reversal of the catabolic phase.[2, 4, 7-10, 12-14] One possible explanation for the lack of agreement may be that the problem arises in such a variety of clinical situations that no one solution can be universally satisfactory. Thus, it is difficult to apply a uniform regimen to the elderly and the young, the previously well-nourished and the depleted, the postherniorrhaphy patient and the one with a fracture, those with pelvic exenteration and those with severe burns.[1]

In this study an attempt has been made to define not only the effect of major trauma on the anabolism of young animals, as measured by growth rate and nitrogen balance, but also the ability of different nutritional programs to influence the changes observed. A chemically defined, synthetic diet[6] was utilized to make the quantitative aspects of the data more precise (Table I). The diet was water soluble and contained the "L" forms of all the essential amino acids and 8 of the nonessential ones, as well as vitamins, salts, trace elements, and glucose. Previous work has demonstrated the ability of this preparation to support normal growth in the experimental animal.[3, 6] The composition of the diet was rigidly controlled, which permitted accurate daily nitrogen balance determinations to be performed. The experimental groups were subjected to a crush injury of sufficient severity to produce major metabolic reaction without proving fatal.

METHODS

Eight groups of 5 male Sprague-Dawley white rats weighing between 125 and 150 grams were used as the experimental animals. All were given the experimental diet, which contained 12.36 mg. of nitrogen per cubic centimeter.

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†Died Feb. 12, 1959.

TABLE I. THE EXPERIMENTAL DIET

WATER-SOLUBLE COMPONENTS (GM./KG. DIET)*							
AMINO ACIDS	WEIGHT (GM.)	VITAMINS	WEIGHT (MG.)	SALTS	WEIGHT (GM.)	FATS AND FAT-SOLUBLE VITAMINS	
L-Lysine · HCl	12.4	Thiamine · HCl	10.0	Sodium chloride	3.16	Vitamin A acetate	1.0 mg.
L-Histadine · HCl H_2O	5.4	Riboflavine	7.5	Potassium hydroxide Gluconolactone	6.17 19.64	Calciferol	0.7 μg
L-Arginine · HCl	7.5	Pyridoxine · HCl	6.3	Magnesium oxide	0.73	a-Tocopherol	5.0 mg.
L-Tryptophan	2.0	Niacin	37.5	Gluconolactone	6.45	2-Methyl-1,4-naphthoquinone	0.42 mg.
L-Phenylalanine	9.0	Inositol	250.0	Ferrous ammonium sulfate	1.40		
L-Leucine	8.0	Choline · HCl	2,500.0	Potassium iodide	0.03	Corn oil†	2.0 ml.
L-Isoleucine	5.0	Ca pantothenate	50.0	Manganese acetate · 4 H_2O	0.26		
L-Threonine	5.0	Biotin	0.3	Zinc benzoate	0.022		
L-Methionine	6.0	Folic acid	0.5	Copper acetate · H_2O	0.015		
L-Valine	7.0	Ascorbic acid	500.0	Cobalt acetate · 4 H_2O	0.009		
		B_{12}	0.1	Ammonium molybdate · 4 H_2O	0.006		
L-Proline	29.9						
Ethyl L-Tyrosinate · HCl	19.8						
Sodium L-Glutamate	60.2						
Sodium L-Aspartate	19.0						
Glycine	4.8						
Ethyl L-Cysteinate · HCl	1.4						
L-Serine	15.5						
L-Alanine	7.5						
Total	225.4	p-Aminobenzoic acid	300.0	Monocalcium fructose 1,6-diphosphate	50.0		

*Total weight brought to 1 kg. by addition of glucose. Each gram equivalent to 4 calories.
†Fat-soluble vitamins dissolved in this volume and fed in equally divided doses 3 times a week per animal.

Fat-soluble vitamins were provided in a corn oil supplement. The animals which were tube-fed received the diet through a soft rubber catheter at 9:00 A.M., 1:00 P.M., 5:00 P.M., and 9:00 P.M. The animals on the ad libitum feeding regimen had diet constantly available. Water intake was never restricted. Urine and feces were collected separately each day from the individual cages at 1:00 P.M., at which time body weights were recorded. The experimental animals were selected from a larger group on the basis of response to a trial period during which they had been tube-fed the diet. All groups within an experiment were equalized on the basis of weight. They were kept in a dark room in which the temperature was maintained at a constant level. The duration of each experimental period was 14 days. The first 4 days constituted a period of base line observation, the fifth day was the operative day on which the injury was inflicted, and the remaining 9 days made up the postoperative period. The injury was produced on the third hour of the operative day after the animals had been given pentobarbital sodium intraperitoneally in the amount of 3 mg. per 100 grams of body weight. It consisted of crushing the upper portion of the right hind limb for 15 seconds with a rubber-shod Payr intestinal clamp, which invariably produced a fracture of the femur.

At the conclusion of the experiments, the animals to be subjected to carcass analysis were sacrificed and the intestinal tracts removed. The carcasses were weighed, placed in plastic bags, and kept frozen until the analyses were performed. They were then homogenized in a Waring Blendor with distilled water to form a 1 to 10 homogenate. The hair was removed by straining through cheesecloth. The final homogenate was readily pipetted and remained in solution for a satisfactory period of time. Aliquots were analyzed for dry weight, by means of a vacuum oven, and for nitrogen content. The remainder of the homogenate was stored in plastic bottles and frozen. Nitrogen determinations were performed by the Perrin modification of the Kjeldahl method.[11] All data relating to the operative day have been included in the postoperative period in the cumulative tables.

The study consisted of 3 experiments, performed in the same environment by the same personnel.

Experiment 1.—Three groups of 5 animals each were used. Rats in all 3 were tube-fed 18 c.c. of the diet for 4 days. Those in one group were then injured on day five, and were continued on 18 c.c. of diet. Rats in a second group were injured on day five, and the diet was increased from 18 to 24 c.c. for the remaining 10 days of the experiment. Those in the third group were not injured and were continued on the 18 c.c. of diet. Daily weights were recorded for all animals, and daily nitrogen balances were determined for the first 2 groups.

Experiment 2.—Three groups of 5 animals were again employed. The first 2 groups underwent exactly the same program as did the first 2 groups in Experiment 1. Rats in the third group were tube-fed 18 c.c. for 4 days, 24 c.c. for the next 10 days, and were not injured. Daily nitrogen balances were calculated

for the individual animals in the first 2 groups, and both daily weights and water intake were recorded for all animals. Carcass analyses were performed on all animals.

Experiment 3.—Two groups of 5 animals were permitted to ingest the experimental diet ad libitum for the duration of the experiment. The animals in the first group were injured on day five. Intake of diet was measured for both groups and daily weights were recorded. The nitrogen balance of the injured animals was determined daily.

RESULTS

During the control periods before the operative day, the weight gains of the animals within each experiment were quite similar (Figs. 1, 2, and 3). After injury, however, in both Experiments 1 and 2 the rate of gain of the animals continuing to receive 18 c.c. of diet by tube was markedly diminished. By

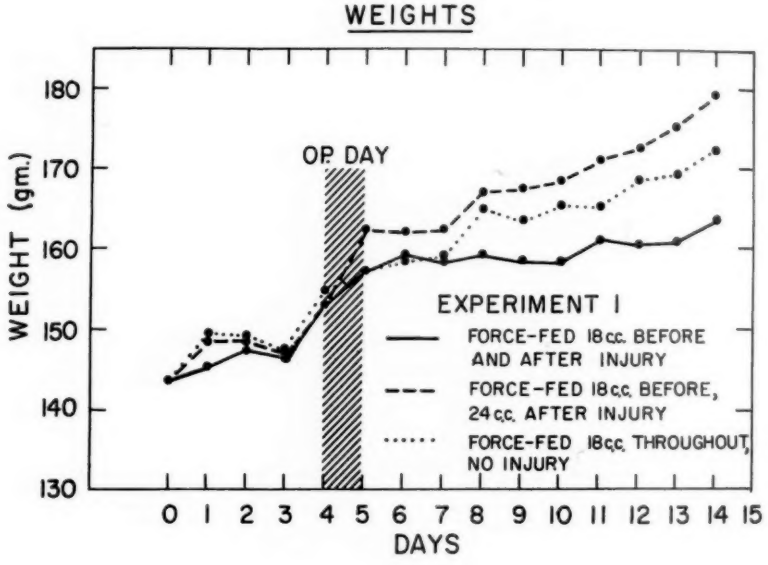

Fig. 1.

comparison, those animals whose diets were increased to 24 c.c. showed a transient increase in the rate of gain, followed by a 2-day lag period, and then resumption of the accelerated growtl. rate. Moreover, the weight of the injured animals on the 24 c.c. regimen increased more rapidly than did that of the uninjured animals receiving 18 c.c. (Fig. 1). In comparison with uninjured animals on the same dietary program, the animals ingesting 18 c.c. prior to injury, and 24 c.c. subsequently, gained less weight for the first 8 days of the postoperative period, but on the ninth postoperative day the weights became equal (Fig. 2).

The amount of diet consumed by the animals fed ad libitum was not affected by injury (Fig. 4), nor was the intake of water (Table II). It is interesting to note that the consumption of diet by these animals was approximately the same as that of the tube-fed animals on the increased (24 c.c.) regimen (Table III). Moreover, the relationship between the weight curves of injured and uninjured ad libitum groups is also quite similar to that between injured and

uninjured force-fed animals. Again, after a transient period of rapid weight gain on the day of operation, no further increase occurred for 2 days, after which growth continued at a normal rate. Equilibration of the 2 groups was

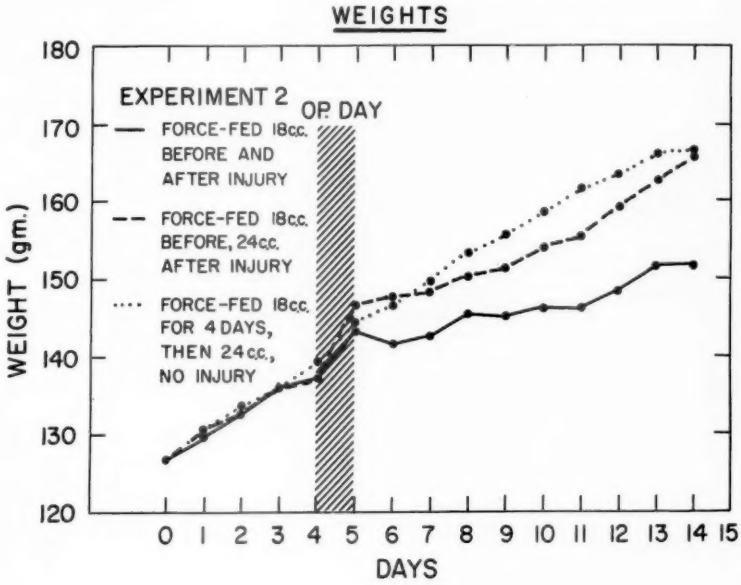

Fig. 2.

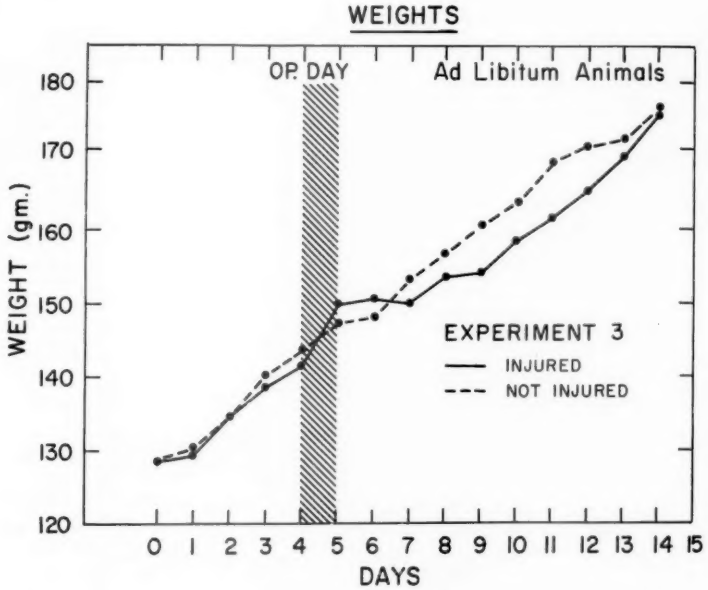

Fig. 3.

reached on the ninth postoperative day. All injured animals show some acceleration of weight gain on the day of operation. The weight gain data are presented in cumulative form in Table IV.

A marked increase in urinary nitrogen excretion occurred in all injured animals (Fig. 5). This increase was of similar magnitude in both the animals

force-fed 18 c.c. before and after injury and those permitted ad libitum access to the diet. The increase in daily urinary nitrogen loss was 27.8 mg. for the former group and 28.4 mg. for the latter (Table V). However, the animals

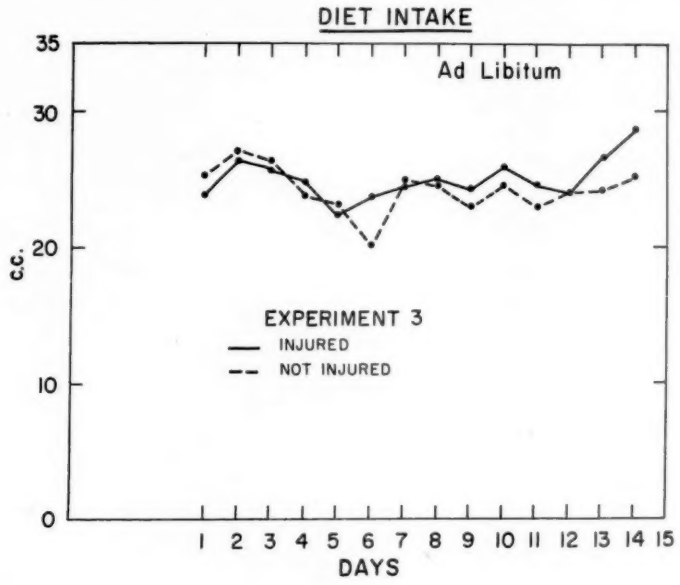

Fig. 4.

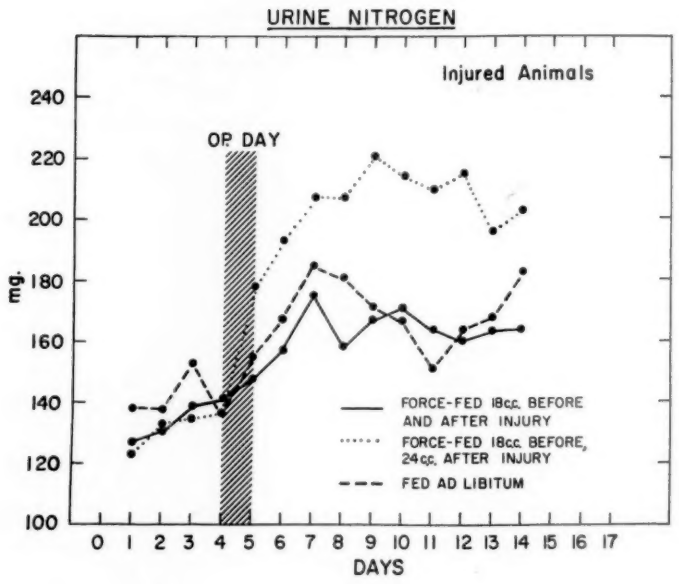

Fig. 5.

whose diet was increased from 18 c.c. to 24 c.c. after injury concomitantly increased their urinary nitrogen excretion by 71.9 mg. per day. Fecal nitrogen was not appreciably affected by injury in the animals on either a constant force-feeding regimen or the ad libitum program, but it did increase 11.9 mg. per day when injury was combined with an increase in diet given by tube. Urinary

TABLE II. WATER INTAKE (C.C./DAY)

	PREOPERATIVE	POSTOPERATIVE
Force-fed 18 c.c. before and after injury	19.1 ± 2.7	23.8 ± 2.5
Force-fed 18 c.c. before, 24 c.c. after injury	18.5 ± 4.3	15.7 ± 2.8
Force-fed 18 c.c. for 4 days, then 24 c.c., no injury	18.5 ± 3.9	16.6 ± 3.3

TABLE III. DIET INTAKE OF ANIMALS FED AD LIBITUM (C.C./DAY)

	PREOPERATIVE	POSTOPERATIVE
Injured	25.2 ± 1.8	24.9 ± 1.0
Not injured	25.7 ± 1.3	23.7 ± 1.7

TABLE IV. CUMULATIVE WEIGHT GAIN (GM.)

	PREOPERATIVE (4 DAYS)	POSTOPERATIVE (10 DAYS)
Experiment 1		
a. Force-fed 18 c.c. before and after injury	9.8 ± 1.0	10.6 ± 4.2
b. Force-fed 18 c.c. before, 24 c.c. after injury	9.8 ± 0.6	26.0 ± 1.6
c. Force-fed 18 c.c. throughout, no injury	11.2 ± 1.4	18.6 ± 0.6
Experiment 2		
a. Force-fed 18 c.c. before and after injury	10.6 ± 1.4	14.0 ± 1.4
b. Force-fed 18 c.c. before, 24 c.c. after injury	10.6 ± 1.4	28.8 ± 2.0
c. Force-fed 18 c.c. for 4 days, then 24 c.c., no injury	12.8 ± 3.0	27.0 ± 2.6
Experiments 1 and 2 combined		
a. Force-fed 18 c.c. before and after injury	10.2 ± 0.9	12.3 ± 2.2
b. Force-fed 18 c.c. before, 24 c.c. after injury	10.2 ± 0.9	27.4 ± 1.3
Experiment 3		
a. Fed ad libitum before and after injury	13.2 ± 2.2	34.2 ± 4.4
b. Fed ad libitum, no injury	15.6 ± 0.8	32.8 ± 6.6

nitrogen values preoperatively for the animals tube-fed 18 c.c. were not significantly different from those for the ad libitum group consuming 25.5 c.c., but the urinary nitrogen after injury was significantly higher for the tube-fed animals whose intake was raised to 24 c.c. than it was for the injured ad libitum animals. Fecal nitrogen averaged between 12.5 and 16.7 per cent of the total nitrogen excretion, which is consistent with the observations of investigators using more conventional diets. Table VI presents the cumulative data for nitrogen balance in the preoperative and postoperative periods. The effect of the 6 c.c. increase in diet in mitigating the diminution in anabolism due to the injury can be seen from the results of Experiments 1 and 2. While the animals continuing to receive 18 c.c. after injury had a 31.6 mg. per day drop in nitrogen balance positivity, those whose intake was increased to 24 c.c. demonstrated only

a 9.8 mg. per day decrease. That this was not attributable simply to transient retention of the increase in diet is implied by the daily urinary nitrogen levels (Fig. 5) which do not show an increasing tendency to lose nitrogen late in the

TABLE V. NITROGEN EXCRETION (MG./DAY)

	URINE			FECES		
	PRE-OPERATIVE	POST-OPERATIVE	CHANGE	PRE-OPERATIVE	POST-OPERATIVE	CHANGE
Experiment 1						
a. Force-fed 18 c.c. before and after injury	140.5 ± 8.8	167.7 ± 11.4	27.2 ± 7.2	20.9 ± 1.8	24.0 ± 2.0	3.1 ± 2.6
b. Force-fed 18 c.c. before, 24 c.c. after injury	133.6 ± 5.0	206.6 ± 6.0	73.0 ± 7.1	20.8 ± 1.2	33.9 ± 3.2	13.1 ± 2.5
Experiment 2						
a. Force-fed 18 c.c. before and after injury	129.1 ± 4.3	157.5 ± 4.6	28.4 ± 3.6	20.6 ± 1.0	24.8 ± 0.9	4.2 ± 1.0
b. Force-fed 18 c.c. before, 24 c.c. after injury	130.3 ± 3.9	201.2 ± 6.2	70.9 ± 8.0	23.9 ± 2.4	34.6 ± 3.7	10.7 ± 2.9
Experiments 1 and 2 combined						
a. Force-fed 18 c.c. before and after injury	134.8 ± 4.9	162.6 ± 6.3	27.8 ± 4.0	20.8 ± 1.0	24.4 ± 1.1	3.7 ± 1.4
b. Force-fed 18 c.c. before, 24 c.c. after injury	132.0 ± 3.2	203.9 ± 4.3	71.9 ± 5.4	22.4 ± 1.3	34.3 ± 2.4	11.9 ± 1.9
Experiment 3						
Fed ad libitum before and after injury	140.9 ± 9.2	169.3 ± 5.5	28.4 ± 7.5	29.6 ± 2.3	29.6 ± 1.6	0 ± 1.4

TABLE VI. NITROGEN BALANCE (MG./DAY)

	PREOPERATIVE	POSTOPERATIVE	CHANGE
Experiment 1			
a. Force-fed 18 c.c. before and after injury	61.1 ± 8.5	30.6 ± 11.8	-30.5 ± 8.4
b. Force-fed 18 c.c. before, 24 c.c. after injury	68.2 ± 5.5	56.1 ± 4.9	-12.1 ± 6.3
Experiment 2			
a. Force-fed 18 c.c. before and after injury	72.9 ± 4.5	40.1 ± 5.0	-32.8 ± 3.1
b. Force-fed 18 c.c. before, 24 c.c. after injury	68.3 ± 5.9	60.8 ± 8.0	- 7.5 ± 6.3
Experiments 1 and 2 combined			
a. Force-fed 18 c.c. before and after injury	67.0 ± 4.8	35.4 ± 6.4	-31.6 ± 4.5
b. Force-fed 18 c.c. before, 24 c.c. after injury	68.3 ± 4.1	58.5 ± 4.7	- 9.8 ± 5.8
Experiment 3			
Fed ad libitum before and after injury	133.5 ± 11.5	109.5 ± 10.6	-24.0 ± 4.8

postoperative period. Nevertheless, the ad libitum group on a postoperative intake of 24.9 c.c. had a positive balance of 109.5 mg. per day as opposed to 58.5 mg. per day for the force-fed animals receiving 24 c.c.

Further evidence for the greater efficacy of ad libitum versus tube feeding similar amounts of diet is seen in Table VII. In the postinjury period the animals fed ad libitum retained an average of 1,095 mg. of nitrogen for the 10-day period, while the tube-fed group receiving 24 c.c. retained only 584.5 mg. This latter figure, however, does represent a significant increase over the 353.6 mg. retained by the animals maintained on the 18 c.c. force-fed diet after injury.

TABLE VII. CUMULATIVE WEIGHT GAIN AND NITROGEN RETENTION

	PREOPERATIVE (4 DAYS)			POSTOPERATIVE (10 DAYS)		
	WEIGHT GAIN (W) (GM.)	NITROGEN RETENTION (N) (MG.)	N/W	WEIGHT GAIN (W) (GM.)	NITROGEN RETENTION (N) (MG.)	N/W
Experiment 1						
a. Force-fed 18 c.c. before and after injury	9.8 ± 1.0	244.3 ± 34.2	24.9 ± 2.6	10.6 ± 4.2	306.1 ± 126.5	28.9 ± 4.3
b. Force-fed 18 c.c. before, 24 c.c. after injury	9.8 ± 0.6	272.6 ± 22.0	27.8 ± 2.7	26.0 ± 1.6	561.0 ± 48.5	21.6 ± 1.5
Experiment 2						
a. Force-fed 18 c.c. before and after injury	10.6 ± 1.4	291.6 ± 18.2	27.5 ± 3.5	14.0 ± 1.4	401.0 ± 50.0	28.6 ± 2.9
b. Force-fed 18 c.c. before, 24 c.c. after injury	10.6 ± 1.4	273.2 ± 23.5	25.8 ± 5.7	28.8 ± 2.0	608.0 ± 80.2	21.1 ± 1.4
Experiments 1 and 2 combined						
a. Force-fed 18 c.c. before and after injury	10.2 ± 0.9	268.0 ± 19.4	26.2 ± 2.2	12.3 ± 2.2	353.6 ± 68.0	28.8 ± 2.6
b. Force-fed 18 c.c. before, 24 c.c. after injury	10.2 ± 0.9	272.9 ± 16.1	26.8 ± 3.2	27.4 ± 1.3	584.5 ± 46.9	21.4 ± 1.0
Experiment 3						
Fed ad libitum before and after injury	13.2 ± 2.2	534.0 ± 45.9	40.5 ± 5.3	34.2 ± 4.4	1,095.0 ± 106.4	32.0 ± 3.4

Moreover, when the ratio of miligrams of nitrogen retained per cubic centimeter of diet ingested is calculated, it appears that the 24 c.c. force-fed diet is more efficient than the 18 c.c. diet in promoting nitrogen retention. The figures obtained for this ratio in the postoperative period are 1.96 with the 18 c.c. diet and 2.44 for the 24 c.c. diet.

Examination of the ratio of nitrogen retained per gram of weight gained is of interest. In the preoperative period the similarity among the different force-fed groups on the same intake is indicative of the relative constancy of this ratio under basal conditions in matched animals. The ratio observed preoperatively in the ad libitum groups is 54 per cent higher than that of the force-fed animals, which suggests that a greater proportion of the body weight exists

TABLE VIII. CARCASS ANALYSIS

	WEIGHT (GRAMS)	% NITROGEN	% WATER
Force-fed 18 c.c. before and after injury	133.2 ± 2.1	2.4 ± 0.13	77.8 ± 1.0
Force-fed 18 c.c. before, 24 c.c. after injury	147.1 ± 3.0	2.3 ± 0.07	76.7 ± 1.2
Force-fed 18 c.c. for 4 days, then 24 c.c. no injury	147.9 ± 3.1	2.5 ± 0.02	77.1 ± 1.7

as protein in animals fed by the former technique. The results of the carcass analyses (Table VIII) indicate that the percentage of nitrogen and water in the body are the same in those tube-fed animals given 18 c.c. before and after injury, those given 18 c.c. before and 24 c.c. after injury, and those given 18 c.c. for 4 days and 24 c.c. for the following 10 days without injury.

DISCUSSION

The ability of major trauma to alter protein metabolism in the young animal is clearly manifested by retardation of growth rate and diminution of the positivity of nitrogen balance. Nevertheless, it appears that these effects can be moderated to the benefit of the organism by a balanced diet supplied in adequate amounts. The effect of injury on growth rate is influenced by the nutritional status of the animal; thus, when the growth rates of injured and uninjured animals on an 18 c.c. diet are compared, a marked lag in growth of the former is observed, while the difference in those receiving 24 c.c. is considerably less in extent and duration. The data on nitrogen balance support the hypothesis that the injured animal can utilize balanced dietary supplements for growth. It would be erroneous to maintain that all of the additional nutrients are retained, however, since there is some loss in feces and urine. Despite this, it cannot be argued that the weight gain of the animals receiving increased diet after trauma is due simply to water retention, with the exception of the transient retention on the day of operation. The carcass analyses performed after the experiment was terminated clearly indicate identical proportions of nitrogen and water in injured animals receiving increased intake, in uninjured animals, and in injured animals not receiving added nutrients.

Significant differences exist between the way the organism utilizes similar amounts of diet when it is provided ad libitum and when it is tube-fed 4 times a day. Weight gain is 24.8 per cent greater and nitrogen retention 87.3 per cent higher in the ad libitum group than in the force-fed groups of Experiments 1 and 2 combined. Apparently, the mode of administration of nutrients is important in determining their ultimate effectiveness, and the result obtained with one technique cannot be considered to apply to others.

SUMMARY

The effect of severe trauma on the growth and nitrogen balance of young animals under different dietary regimens has been studied. A deleterious effect of injury on these parameters has been observed. However, the provision of adequate nutrients after trauma appears to be worth while, for much of the

decrease in growth rate and nitrogen retention can be prevented. While diet may not be utilized as efficiently in the postinjury period as it is under normal conditions, there is an advantage to the maintenance of a high level of intake. There is also strong indication that ad libitum ingestion is preferable to 4 daily tube feedings.

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BIOPSY OF THE AMPULLA OF VATER FOR DEMONSTRATION OF ORGANIC STENOSIS

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STENOSIS of the sphincter of Oddi is being recognized with increasing frequency as a cause of persistent or recurrent symptoms in some patients after cholecystectomy.[1-3]

Although Henderson[6] and Florken[5] suggested the possibility of benign organic stenosis of the distal common bile duct, Delfor Del Valle[4] was the one who, in 1928, presented the best clinical and pathologic description of stenosing lesions of the main biliary ducts. Del Valle stressed the occurrence of total as well as partial obstructions of the common bile duct resulting from chronic cicatricial inflammation. This obstruction was noted with or without associated common duct stone and was described as sclerosing choledocho-odditis (sclero-retractile choledocho-odditis). The concurrent development of the concept of purely functional sphincteral phenomena (biliary dyskinesia due to sphincter spasm) not only has resulted in considerable confusion between the functional disorders of this region and those of organic pathogenesis, but also has distracted from further study of the organic lesions of the area.

In order to investigate the organic lesions of the ampulla of Vater in patients with symptoms and operative findings[7] suggesting stenosis of this region, we decided to perform operative biopsies in a group of patients.

The lack of available documentation of the normal histologic appearance of the periampullary area of the common duct required a preliminary anatomic and histologic study of this region. Accordingly, the gross and microscopic anatomy of the ampulla was investigated in 3 groups of patients:

1. Sections were made from the distal common duct and ampulla of 20 cadavers (15 adults and 5 children), of ages from 1 month to 71 years. Death in these patients had been from neither pancreatic nor biliary tract disease.

2. Sections were made from the distal common duct and ampulla of the resected head of the pancreas in 2 patients who had undergone pancreatic excisions for cancer of the stomach which had become adherent to the pancreas.

3. Sections were made of biopsy specimens of the ampulla of Vater and sphincter of Oddi excised from 23 patients operated upon for biliary tract disease who, at the time of exploratory operation, displayed such marked narrowing of the ampulla of Vater that a 3 mm. dilater could not be passed from the choledochostomy opening through the ampulla into the duodenum.

In the autopsy specimens, the sections were made transversely to the long axis of the common duct in 6 cases, longitudinally or parallel to the axis of the

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common duct in 4 cases, and both longitudinally and transversely in 10 cases. The transverse sections were made at intervals of 3 to 7 mm. and the longitudinal sections in fragments of 1 cm.

The necropsy material and the 2 surgical specimens of patients without biliary tract disease demonstrated no inflammatory infiltration, muscular hypertrophy, or fibrosis, except for one, in which there was an inflammatory process involving the ampulla, the common duct, and the pancreatic duct. This was found in a 2-month-old child who had died of fibrinopurulent peritonitis produced by perforation of an intestinal ulcer in severe enterocolitis.

THE NORMAL AMPULLA

A complete description of the histology of the ampulla and distal common duct includes evaluation of the mucosa and the muscular, connective, and elastic tissues (Fig. 1).

Mucosa.—The mucosa in the adult is slightly folded and formed by epithelium and lamina propria or corium. The cells are cylindrical, disposed in 1 layer, with basal elongated nuclei and clear transparent cytoplasm. The lamina propria of the mucosa is formed by vascularized connective tissue containing numerous mucoid-type glands found chiefly at the posterior wall of the ampulla (Fig. 2). Glandular formations also occur in the hepatic and common ducts. The duodenal mucosa is suddenly interrupted at the level of the ampullar ostium and replaced by the ampullar mucosa. Cellular inflammatory infiltration is almost never found in the lamina propria of the mucosa. Among 22 patients without stenosis of the ampulla, only 1 presented inflammatory infiltration.

Muscular Tissue.—The muscular tissue is found at the distal end of the ampulla quite near the external opening and also between the glands. The fibers are predominantly circular in type, although longitudinal and even oblique bundles can be discerned. These fibers are more numerous and better developed at the anterior wall of the ampulla.

Starting from the distal end of the ampulla, the muscle fibers progressively increase in number and caliber until the whole circumference is encompassed (Fig. 3). The common duct is also encircled at its intramural portion (inferior sphincter of the common duct) by muscle fibers, predominantly circular in type, which gradually disappear as the duct goes up toward the liver. At the distal intrapancreatic portion, well-developed muscle bundles can be found (superior sphincter of the common duct). The muscle fibers, normally more abundant at the posterior wall of the common duct near the duodenum, become numerous also at the anterior wall as the duct goes away from the duodenum. They progressively disappear, and only rare fibers are found at the supraduodenal and proximal portion of the retropancreatic common duct.

The pancreatic duct is also surrounded by longitudinal and circular muscle fibers, but only for a short distance and at the distal end near the junction with the common duct. Beyond this point, the musculature is almost absent and only rare fibers can be demonstrated between the pancreatic and common bile ducts.

Fig. 1.

Fig. 2.

Fig. 3.

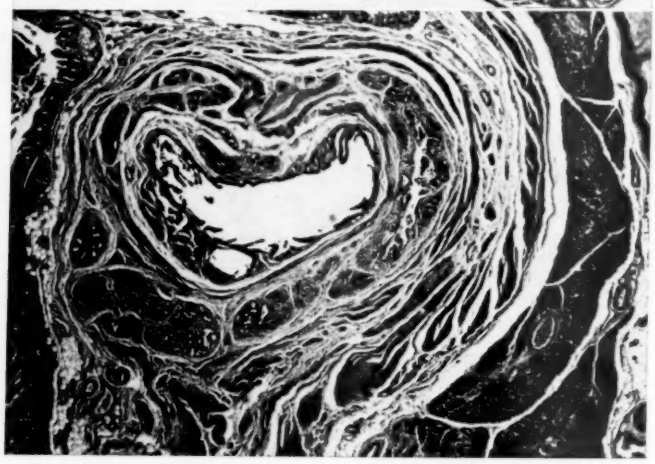

Fig. 1.—Normal papilla (autopsy specimen).
Fig. 2.—Posterior wall of the ampulla with its normal glands.
Fig. 3.—The 2 ducts encircled by the sphincter of Oddi. Muscle fibers between both ducts.

In some cases, there seems to be a complete separation between the ampullar and duodenal musculatures. In others, however, the fibers are mixed, making it difficult and even impossible to identify the individual components. In the child, the fibers are thinner and less numerous but the arrangement is the same as in the adult.

Elastic Tissue.—The elastic tissue is sparse at the level of the ampulla and becomes progressively more abundant in the proximal common duct. Here it constitutes one of the main elements of the wall and forms a tight mesh with thin fibers toward the region of the lumen of the duct, and a loose mesh with thick fibers toward the external region of the duct. The muscular and elastic tissues have an inverse distribution in the common duct. This relationship is similar in the adult and the child, although all the fibers are, in general, less developed in children.

Connective Tissue.—At the ampulla the connective tissue is not dense, but loosely fills the space between the other tissues. At the common duct and pancreatic duct, it forms a fibroelastic layer which, with the elastic tissue, constitutes a very important element of the wall.

PATHOLOGY OF THE DISTAL COMMON DUCT

The histologic changes noted in the 23 biopsy specimens obtained at operation from patients with stenotic sphincter of Oddi include muscular hypertrophy, mucosal proliferation, glandular hyperplasia, fibrosis, and cellular infiltration.

There was muscular hypertrophy in 20 of the 23 patients studied. In 7 of these cases, the hypertrophy was intense with a great proliferation of the muscle fibers that occupied almost all the ampullar wall, invaded the mucosa, and compressed the glandular elements (Figs. 4 and 5). In 9 cases the hypertrophy was of moderate intensity and in the other cases it was minimal. Muscular hypertrophy was the only alteration found in 4 cases, while in the others it was associated with other pathologic changes such as mucosal proliferation, fibrosis, and inflammatory infiltration.

Mucosal proliferation was observed in 4 of the 23 biopsy specimens (Figs. 6 and 7). In one of these, the mucosal overgrowth was marked and directed toward the ampullar lumen. Papillary mucosal projections were very evident. The gross appearance in these cases was that of a papilloma with its villous projections occupying the ampullar lumen and protruding into the duodenum through the papilla. These villous projections were lined with a cylindrical epithelium similar to the one normally found in this region. The epithelium covered a central connective tissue core containing blood vessels and some muscle fibers. There was also intense muscular hypertrophy and moderate connective tissue proliferation. The pathologic diagnosis was papilloma of the ampulla. In 2 other cases there was less marked villous mucosal proliferation.

The mucosal glands appeared normal or showed some tendency toward cystic degeneration in 12 cases. In 3 cases the glands were less numerous and were compressed by the hypertrophic muscle tissue. In another case, however, there

was intense hyperplasia of the glandular tissue, with cystic formations at the distal end of the glands which were lined by cylindrical and mucoid cells.

Intense fibrosis was observed only 3 times, being associated once with muscular hypertrophy and another time with lymphocytic infiltration. In 2 cases, the fibrosis was moderate and in 3 other cases it was very slight and always associated with another pathologic process which was the dominant histologic finding.

Fig. 4.

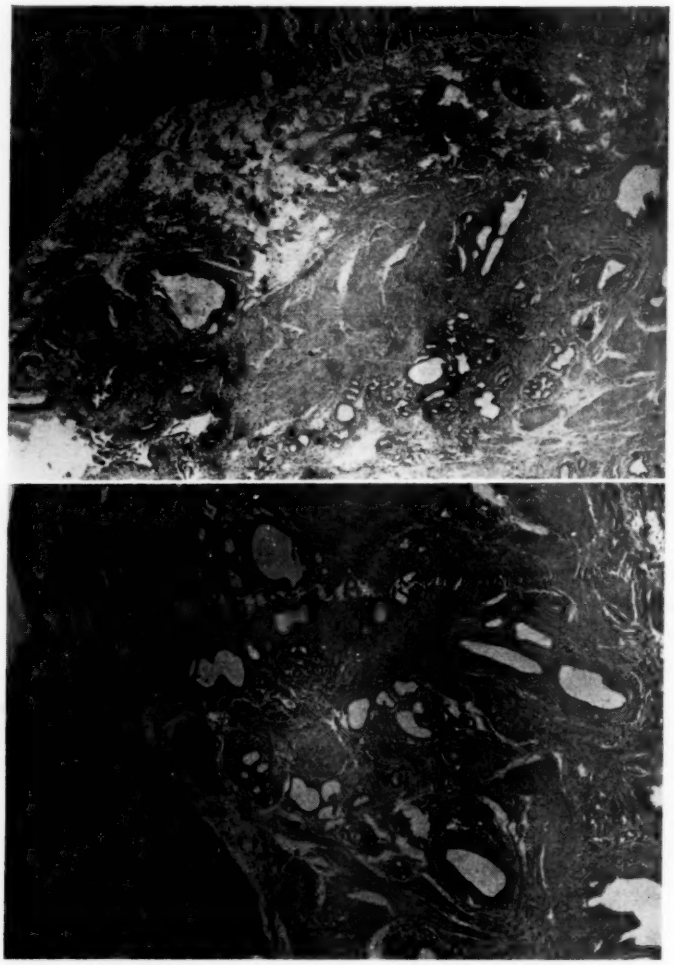

Fig. 5.

Fig. 4.—Muscle hypertrophy and compressed glandular elements in the wall of the ampulla. Some of the glands have a cystic appearance.

Fig. 5.—Higher power view of the section in Fig. 4.

Cellular inflammatory infiltration of lymphocytes, plasma cells, and eosinophils, in proportions varying from case to case, was predominantly localized at the mucosa, although it was sometimes observed between the muscular and connective tissues. Only once was the cellular infiltration marked and, in this case, was associated with a severe muscular hypertrophy. In 3 cases, the cellular infiltration was moderate and in 8, slight.

DISCUSSION

The etiologic relationships between biliary dyskinesia, odditis (stenosis of the papilla), cholecystitis, and cholelithiasis are controversial and speculative. At present, our knowledge of periampullar pathology is so limited that theorizing is unwarranted. Although biliary dyskinesia may exist as a clinical entity, we have been unable to define its clinical or roentgenographic pattern during an extensive clinical experience in biliary tract surgery over a period of 20 years.

Fig. 6.

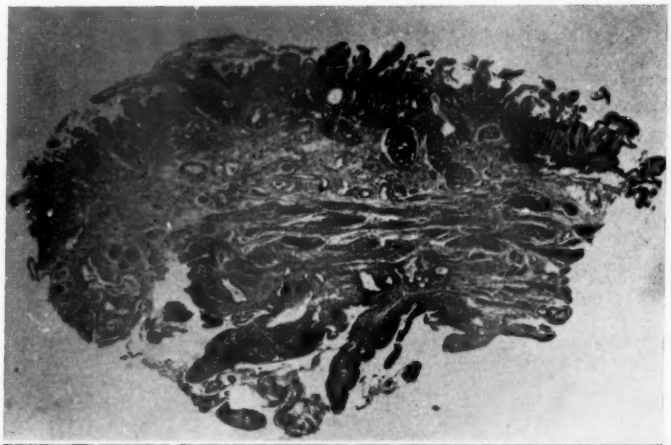

Fig. 7.

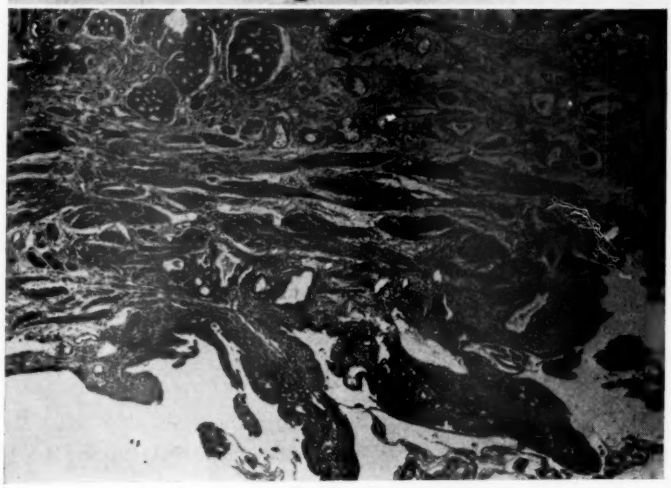

Fig. 6.—Surgical specimen of the papilla showing moderate muscular hypertrophy, proliferation of the mucosal folds, and cellular infiltration.

Fig. 7.—Higher magnification of the photomicrograph in Fig. 6.

The stenosing organic lesions seem well demonstrated in our pathologic study.

The incidence or the frequency of the stenosis of the sphincter of Oddi in patients with biliary disease is not yet established.

It should be pointed out that in our series, in 438 biliary operations between 1950 and 1953, we found 3 cases of stenosis and in 511 operations between 1954 and 1957 we found 20 cases proved by the histologic sections.

As it was emphasized by Cattell,[1] with the increasing interest in sphincterotomy it is important to point out that this operation should not be used indiscriminately and that when employed it should not be regarded lightly.

In our 23 biopsies we had no complications and all patients were discharged from the hospital in about 2 weeks after the operation.

The steps in the procedure of biopsy of the ampulla are shown in Fig. 8.

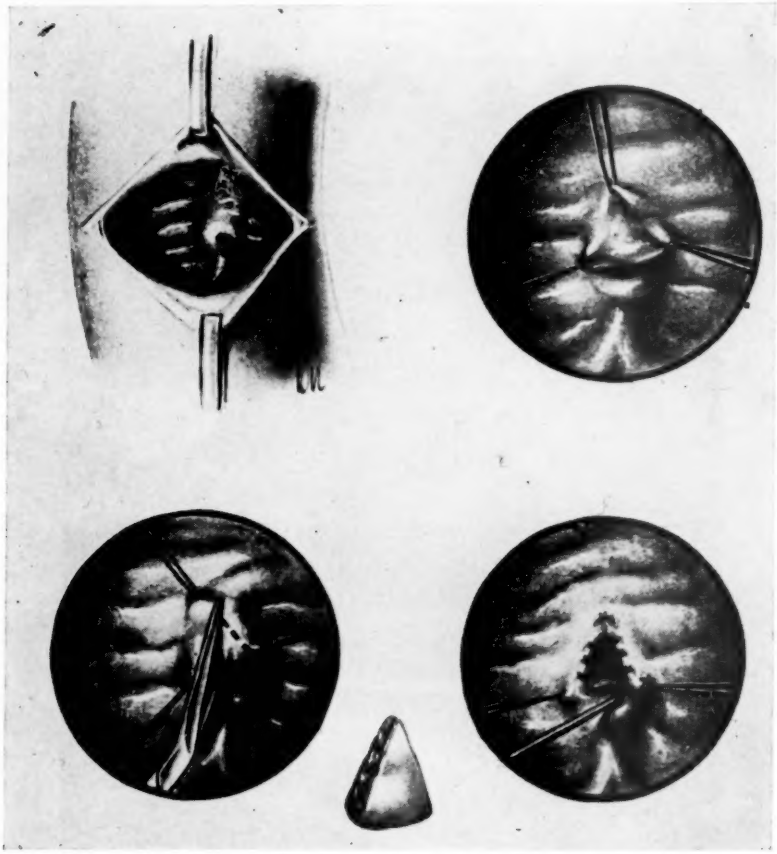

Fig. 8.—Steps in the procedure of biopsy of the ampulla of Vater.

The ampulla was exposed by the routine duodenotomy and its anterior wall excised. The incision was carried upward in an extension of 15 mm. Bleeding was controlled by suturing the edges of the mucosa of the ampulla to the mucosa of the duodenum or by simple compression. The opening of the duct of Wirsung must be identified precisely before suturing the duodenal mucosa to the ampulla in the left side.

If the pancreatic duct cannot be identified, no sutures are tied in this side of the sphincterotomy in order to avoid obliteration of the duct of Wirsung.

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EFFECT OF SURGICAL PITUITRIN UPON PORTAL AND HEPATIC CIRCULATION

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FOR some time it has been known that the intravenous administration of posterior pituitary extract to laboratory animals brings about a decrease in portal venous pressure.[1, 4, 6] This effect has been generally attributed to vasoconstriction of the preportal splanchnic arterioles. Interest in the action of Pituitrin upon the portal and the hepatic circulation has been revived by the apparently successful use of this drug in the control of massive hemorrhage from esophageal varices.[5, 7]

This study was undertaken in order to determine by direct measurement the effects of Pituitrin upon portal and hepatic blood flow as well as upon portal venous pressure.

METHODS

Adult mongrel dogs weighing from 14 to 20 kilograms were used. They were anesthetized with intravenous thiopental sodium and rhythmic insufflation of the lungs was carried out with oxygen administered through an endotracheal tube. The blood pressure was recorded on a mercury manometer from a catheter inserted into a femoral artery. Saturation of portal venous oxygen was determined at intervals in some animals by the Roughton-Scholander technique. All animals were maintained throughout each experiment at normal or near normal levels of body temperature and blood volume. Studies included in this report were carried out as definitive investigations after a large preliminary experience with the direct measurement of portal and hepatic circulation and the effect of various drugs upon portal blood flow.

Portal blood flow was determined by a method which is described in detail in another report.[3] The portal vein was exposed through a right thoracoabdominal incision. It was divided and the 2 divided ends were cannulated. Blood was allowed to flow by gravity from the distal portal bed into a graduated burette from which it was returned into the proximal portal vein by means of a Sigmamotor pump. This pump was regulated so as to return the blood at the same rate as it was delivered into the burette. By stopping the pump and recording the time interval required for the accumulation of a given volume of blood in the burette, we could calculate the portal flow.

The condition of each animal was allowed to stabilize 15 minutes before any experimental procedure was instituted. Three groups of animals were studied.

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In the first group of 3 animals, portal flows were measured before and after a single intravenous injection of 4 U. of surgical Pituitrin diluted with 2 c.c. of saline. In the second group of 3 animals, portal flows were measured to determine the effect of repeated injections of 4 U. of surgical Pituitrin given every 10 minutes over a period of 1 hour. Similar studies were carried out in the third group comprised of 4 animals in which a continuous intravenous infusion of 40 U. of surgical Pituitrin in 40 c.c. of saline was administered over a 30-minute period. In still another group the response of portal pressure was studied. In 2 of these animals an injection of 4 U. of surgical Pituitrin was given, in another 2 repeated injections of surgical Pituitrin were given every 10 minutes over a period of 1 hour, and in still another 2 a 30-minute infusion of 40 c.c. of saline containing 40 U. of Pituitrin was administered.

Hepatic blood flows were determined by isolation of the inferior vena cava above the diaphragm and in the upper abdomen through a right thoracoabdominal incision in the tenth intercostal space. Hemostasis was maintained by the use of electrocautery. Umbilical tapes were placed about the vena cava above the diaphragm and in the upper abdomen cephalad to the level of entry of the adrenal veins. One femoral and both external jugular veins were exposed. The animal was heparinized by the intravenous administration of 1 mg. sodium heparinate per kilogram of body weight. A shunt from the inferior to the superior vena cava was then constructed with three sixteenths inch polyethylene tubing. The distal end of the tube was inserted into the inferior vena cava at the level of the renal vein through an incision in one femoral vein, and the proximal end was inserted into the superior vena cava through one of the external jugular veins. A multiholed five sixteenths inch polyethylene catheter was placed in the vena cava below the diaphragm. The vena cava was ligated above and below the points of entry of the hepatic veins so that the catheter would permit free gravity drainage of the total hepatic venous return into a burette (Fig. 1). The burette was kept approximately 10 cm. below the level of the vena cava in order to insure free gravity drainage without collapse of the vena cava or hepatic veins. Blood from the burette was returned to the animal by a Sigmamotor pump and a catheter previously placed into the superior vena cava through the other external jugular vein. The burette and the extracorporeal tubing were primed with fresh heparinized blood from a donor dog prior to each experiment. The pump was adjusted so that blood would be returned to the superior vena cava at the same rate it drained into the burette. By momentarily stopping the pump, one could observe the period of time necessary for the accumulation of 50 c.c. of blood in the burette and thus calculate the hepatic blood flow.

Hepatic flows were measured in 7 animals after a 15 minute period of stabilization. In the first 3, the response of hepatic blood flow to the single injection of 4 U. of surgical Pituitrin was studied. In another 4 animals, similar studies were carried out during a 30-minute period of infusion of 40 c.c. of physiologic saline solution containing 40 U. of surgical Pituitrin.

The response of portal venous pressure and systemic arterial pressure was studied in 2 human subjects. In both portal pressure was measured

manometrically through a plastic tube which had previously been introduced surgically into a branch of the portal vein. In each instance the patient was lying comfortably supine in bed without sedation. Arterial pressure in the brachial artery was followed with a sphygmomanometer.

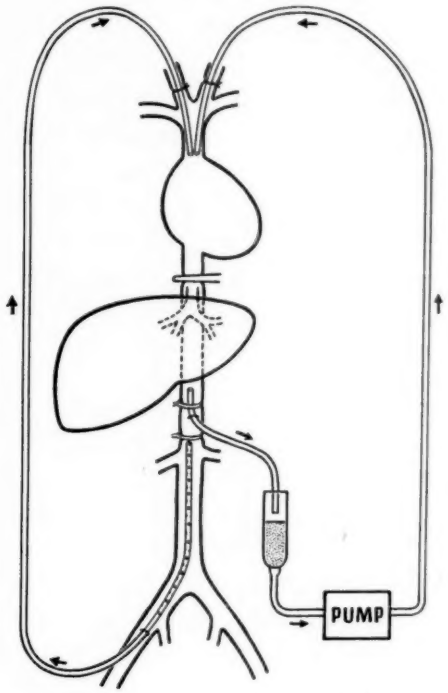

Fig. 1.—Drawing illustrating method for measuring total hepatic venous blood flow.

RESULTS

A single injection of 4 U. of surgical Pituitrin consistently produced a marked depression of portal blood flow. An average decrease of 72 per cent occurred within 2 minutes after the injection, the flow dropping from a mean of 30.5 c.c. per kilogram per minute to 8.6 c.c. per kilogram per minute (Fig. 2). The marked reduction in flow was brief, lasting approximately 5 minutes. The flow returned to approximately normal levels after 15 minutes. After a single injection of 4 units of Pituitrin the portal pressure dropped nearly 26 per cent from an average of 138 to 102 mm. H_2O. It did not return to the normal level until approximately 25 minutes after the injection. Hepatic blood flow decreased less than portal blood flow after a single injection of Pituitrin and recovery was much more rapid.* In these animals the average hepatic blood flow decreased 34 per cent from 36.4 to 24.1 c.c. per kilogram per minute. It returned to a normal level in nearly 3 minutes.

Multiple injections of 4 U. of Pituitrin every 10 minutes produced the same type of response (Fig. 3). There was a precipitous fall in portal flow after each injection with a fairly rapid recovery to normal or near normal levels. Each injection was also followed by a prompt drop in portal pressure. No

*In all of the studies carried out up to the present time the hepatic blood flow under normal circumstances has averaged 39.7 c.c. per kilogram per minute.

evidence of tachyphylaxis was observed in any of the animals; this was true with regard to both portal blood flow and portal pressure.

From preliminary observations it was evident that small doses of Pituitrin, 10 or 20 U. in 30 c.c. of saline, given by continuous intravenous infusion over

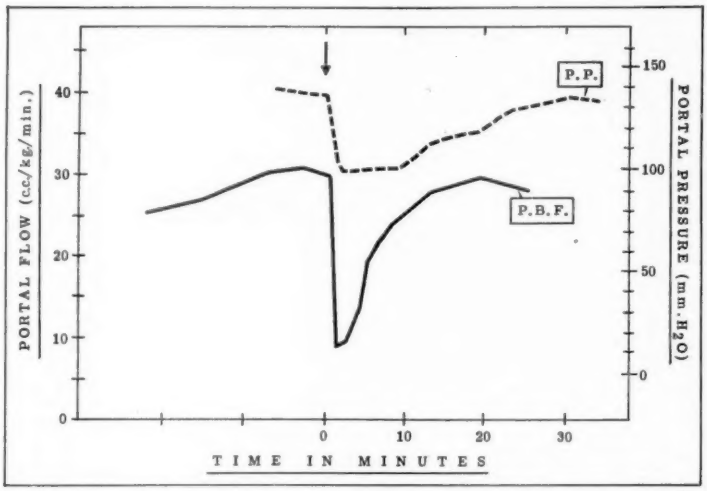

Fig. 2.—Chart showing mean response of portal blood flow and portal pressure to the single injection of 4 U. of surgical Pituitrin. In this and other charts, *P.B.F.* indicates portal blood flow, and *P.P.* portal pressure. Arrow indicates the time of injection.

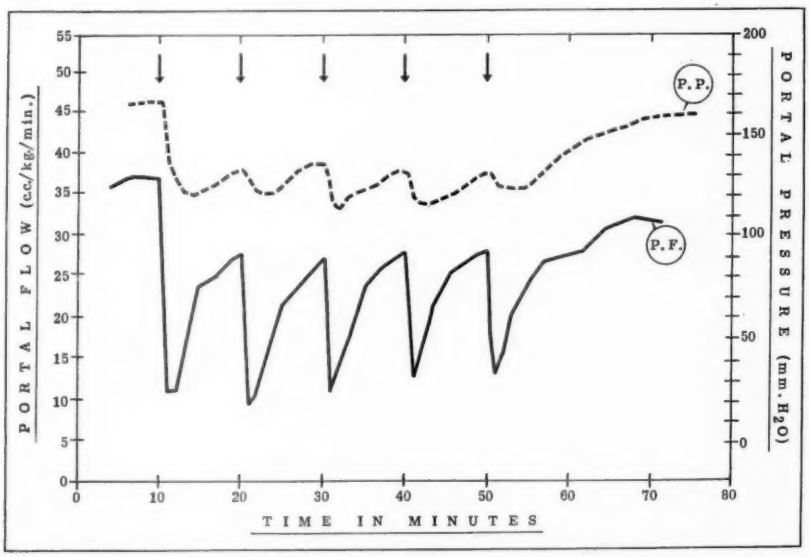

Fig. 3.—Chart showing mean response of portal blood flow and portal pressure to repeated injections of 4 U. of Pituitrin.

a 30-minute period, failed to produce a marked or continuous decrease in portal flow. The larger dose used in this study (40 U. diluted with 40 c.c. of saline), however, produced a marked and sustained decrease in both portal flow and portal pressure during the 30 minutes of infusion (Fig. 4). There was a decrease of approximately 60 per cent in portal blood flow throughout the period of the infusion and a prompt return to a near normal level approximately

15 minutes after the infusion was terminated. Portal pressure similarly remained depressed during the period of infusion and returned slowly toward normal afterward.

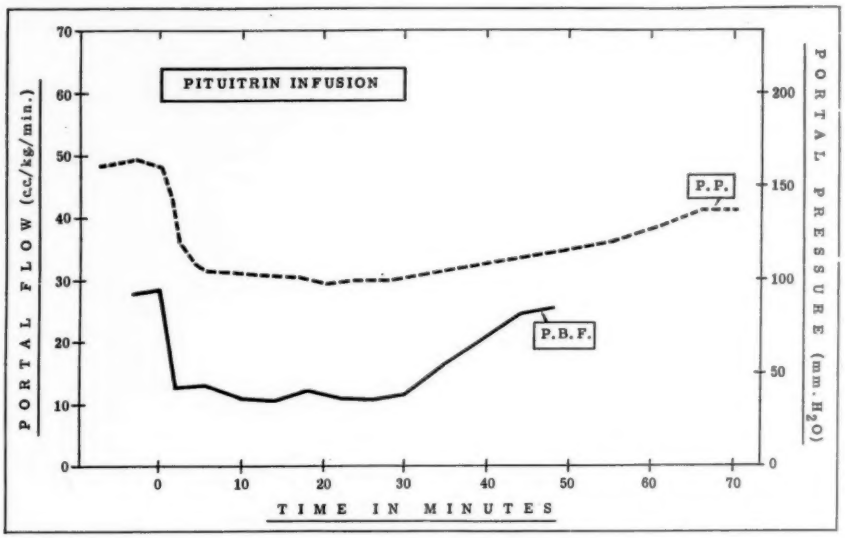

Fig. 4.—Chart showing mean response of portal blood flow and portal pressure to an infusion of 40 U. Pituitrin.

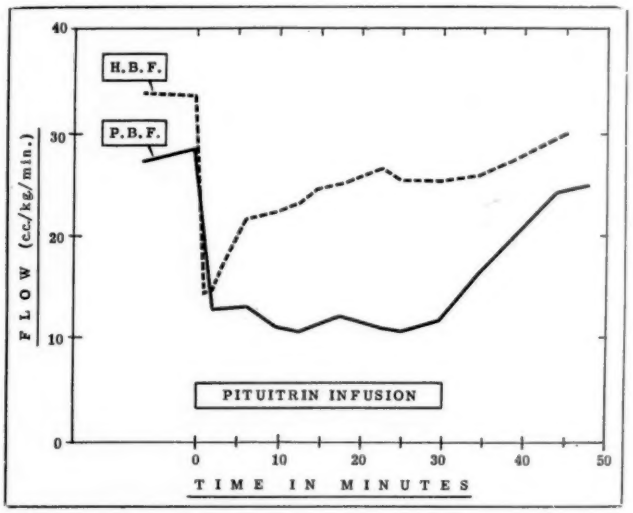

Fig. 5.—Chart comparing response of portal and hepatic blood flow (mean values) to the infusion of 40 U. of surgical Pituitrin. *H.B.F.* signifies hepatic blood flow.

Hepatic blood flow showed a somewhat different response during the period of infusion (Fig. 5). Initially the flow decreased approximately 60 per cent from a level of about 34 to one of approximately 14 c.c. per kilogram per minute. Shortly afterward, however, the flow began to increase and during the remainder of the infusion period was not less than 70 per cent of the normal flow rate.

During the administration of Pituitrin the portal venous oxygen saturation was consistently decreased. The average value before the administration

of Pituitrin was 86.4 per cent and after the injection, 63.8 per cent (Table I). After a single injection of 4 U. of Pituitrin the arterial blood pressure rose on an average to 45 mm. Hg. During the infusion of 40 U. over a half-hour period the rise in blood pressure on the average was only 12 mm. Hg.

Portal pressures were measured on a 7-year-old girl with cavernomatous replacement of the portal vein, splenomegaly, slightly reduced hepatic function, and esophageal varices which had bled. The study was carried out during an uneventful convalescence 2 days after splenectomy and splenorenal anastomosis. Portal pressure preoperatively had been 56 cm. H_2O. At the end of the procedure it was 270. The infusion of 40 U. of Pituitrin in 40 c.c. of 5 per cent dextrose and water over a period of 28 minutes brought about an immediate drop in portal pressure followed by a gradual recovery toward the preinfusion level (Fig. 6). A similar study was made in a 55-year-old man with marked cirrhosis, thrombosis of the portal vein on angiographic study, and marked depression of liver function. This was carried out the day after a plastic tube had been introduced into a branch of the portal vein under local anesthesia. Sixty units of Pituitrin in 60 c.c. of 5 per cent dextrose and water was administered over a period of 32 minutes. Fifteen minutes after the infusion was begun the portal pressure dropped from approximately 75 cm. H_2O to a low of about 38 cm. (Fig. 7). Toward the end of the period of infusion the systemic pressure began to fall and approximately 7 minutes later 3 mg. of Aramine was given intravenously. The portal pressure began to rise about 1 hour and 10 minutes after the infusion had been started.

TABLE I. PORTAL VENOUS OXYGEN SATURATION BEFORE AND AFTER ADMINISTRATION OF PITUITRIN*

NO. OF ANIMAL	WEIGHT (KG.)	OXYGEN SATURATION	
		BEFORE	AFTER
1	18.3	89.4	63.4
2	16.0	86.0	64.2
3	17.9	88.1	72.4
4	18.7	84.0	65.0
5	18.7	80.0	45.0
6	22.4	89.7	78.9
7	27.8	91.6	75.3
8	20.5	82.0	46.5
Mean		86.4	63.8

*Dogs 1 through 6 received a single intravenous injection of Pituitrin, dogs 7 and 8 an infusion.

DISCUSSION

In other studies we have learned that the method of measuring directly the portal blood flow utilized in these experiments is apparently a valid one. Although variation is noted from one animal to another, the portal blood flows in any given animal tend to remain relatively stable over a 1-hour period of study. The method for measuring directly total hepatic blood flow also seems to be valid. Although variations are noted from one animal to another, values in any given animal tend to remain relatively stable during the period of study.

Our studies confirm the observations of others that portal pressure is depressed after the administration of surgical Pituitrin. They demonstrate that

portal and hepatic blood flows are also decreased. In our experience the administration of a single injection of 4 U. of Pituitrin consistently decreases the portal flow to less than one-third of its normal value. This response is brief in duration. The portal pressure is similarly decreased and does not regain its previous level until approximately 10 minutes after the flow has returned to normal. The continued metabolic demands of the abdominal viscera during this period of decreased portal blood flow are reflected in a lowered portal venous oxygen saturation.

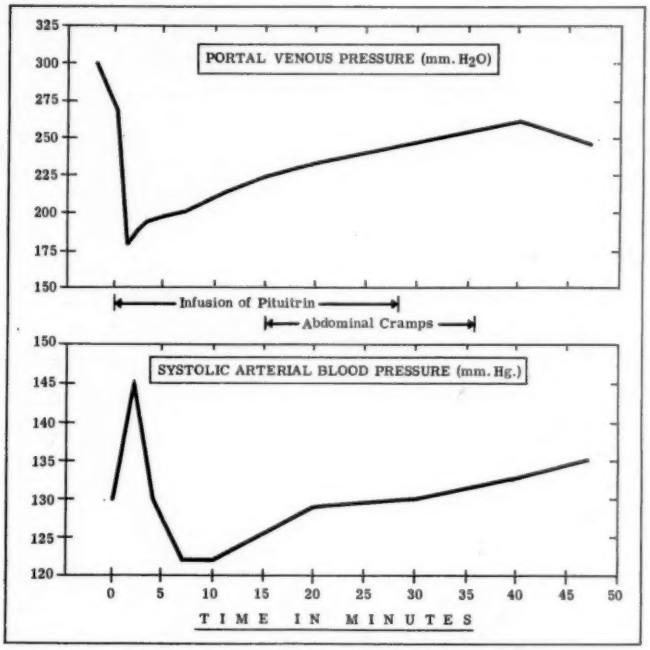

Fig. 6.—Chart showing portal venous pressure and blood pressure response to infusion of Pituitrin in a 7-year-old child 2 days after splenectomy and splenorenal anastomosis.

Our observations on the portal circulation are consistent with the interpretation of others that the lowered portal pressure after the administration of Pituitrin results from a vasoconstrictor response in the preportal splanchnic arterioles. Our method of measuring portal blood flow excludes as a causative factor any possible change in the hepatic circulation per se.

It is interesting that in other studies we found that the intravenous administration of 4 U. of Pitressin produced a moderate decrease in portal blood flow and that 4 U. of Pitocin produced no change in portal blood flow at all. No explanation is available for the more pronounced effect of a similar dose of surgical Pituitrin.

Clark[1] observed that repeated doses of vasopressin evoked successively smaller decreases in portal venous pressure. In our experience repeated doses of Pituitrin evoked no evidence of tachyphylaxis. Repetitive responses seemed identical with the response produced by a single injection.

The repeated injection of Pituitrin does not produce a continuous depression of portal blood flow or portal pressure. The continuous infusion of

Pituitrin, however, is effective in maintaining a satisfactory, persistent decrease both in portal blood flow and in portal pressure. Though a modest rise in systemic arterial blood pressure is noted after each individual injection of Pituitrin, the continuous infusion of Pituitrin causes only a negligible rise in systemic arterial pressure.

The differences in portal and total hepatic blood flow responses to the administration of Pituitrin are of considerable interest. The fact that depression in total hepatic circulation is less pronounced and less well maintained than that of the portal blood flow during the administration of an infusion of Pituitrin is interpreted as being the result of alteration of flow through the hepatic artery. One would suppose that it signifies an increasing flow of blood into the liver from the hepatic artery during the period of infusion. Since only a minimal increase in systemic arterial pressure occurs as a response to the

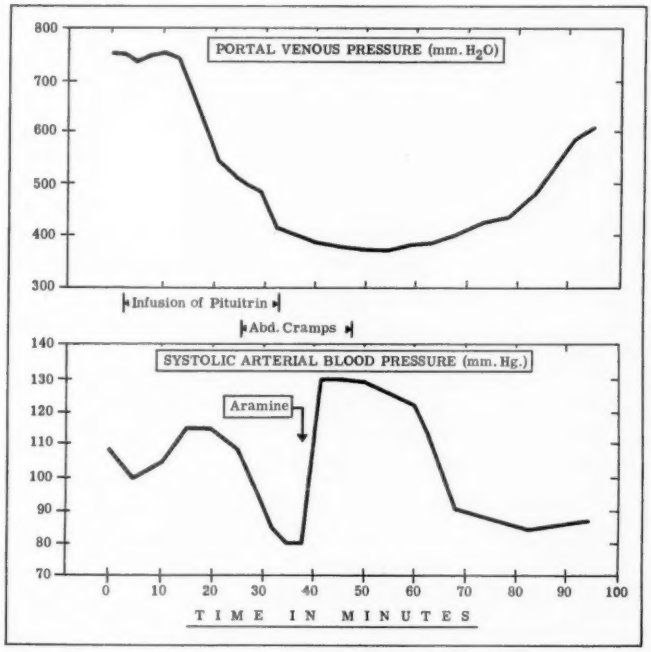

Fig. 7.—Chart showing portal venous pressure and blood pressure response to infusion of Pituitrin in a 55-year-old patient with cirrhosis.

infusion, one would also surmise that the increased hepatic arterial flow into the liver is an indication of decreased pressure in the hepatic sinusoids. The fact that the total hepatic circulation (in the dog, at least) is not maintained at a low level during the entire period of infusion of Pituitrin is reassuring to those who may attempt to control bleeding from esophageal varicosities in patients with badly damaged livers.

Clinical reports would suggest that the intravenous administration of a concentrated solution of Pituitrin may be effective in bringing about cessation of bleeding in patients with esophageal varicosities. In 1956 Kehne, Hughes, and Gompertz[5] gave Pituitrin to 2 patients on several occasions and believed that the treatment was effective in controlling the hemorrhage each time. These authors

also observed that in dogs Pituitrin was more effective in decreasing portal pressure when the portal pressure was artificially raised than in normal animals. More recently, Schwartz and his associates[7] have used an intravenous infusion of Pituitrin to control bleeding varicosities in a somewhat larger series of cases and felt that success was achieved in 88 per cent. They observed at laparotomy that the reduction in pressure occurring after the administration of Pituitrin was approximately equal to that which was noted after a portal-caval anastomosis was completed. They concluded that Pituitrin effectively decreased portal blood pressure and flow without altering hepatic metabolism. Our animal experiments serve as an experimental basis for the continued exploration of a continuous infusion of pituitrin as a possible aid in the control of bleeding esophageal varicosities. Our 2 patients showed a fall in portal pressure during the infusion of Pituitrin. The one with the marked portal hypertension had the greater drop. The fall in arterial blood pressure necessitating the use of a vasopressor was an unexpected occurrence. The patient previously treated successfully by splenorenal shunt had a lesser response. Davis and his colleagues[2] have evaluated the effect of the infusion of Pituitrin on the portal and hepatic circulation in human subjects with a radioisotope method.

SUMMARY

Portal venous pressure, portal venous oxygen saturation, portal blood flow, and total hepatic blood flow have been studied in anesthetized dogs given single or repeated injections of surgical Pituitrin and in dogs given a continuous infusion of Pituitrin. Following a single injection of surgical Pituitrin a prompt, marked, but transient decrease in portal flow occurs. A similarly prompt, marked, but somewhat more sustained decrease in portal pressure is noted. The saturation of the portal venous blood falls. Hepatic blood flow decreases somewhat less than portal blood flow and the response is even more brief. Similar responses are observed repetitively when repeated injections of Pituitrin are given. With the continuous infusion of Pituitrin, portal blood flow drops to a low level and is maintained. A similarly sustained decrease in portal pressure is noted. Hepatic blood flow falls immediately but soon afterward rises to a level within 30 per cent of the normal value. A negligible increase in arterial blood pressure accompanies the infusion of Pituitrin. The difference in the response of the portal and of the hepatic blood flow to the infusion of Pituitrin is interpreted on the basis of the contribution of hepatic arterial inflow into the liver. These observations suggest that during the infusion, hepatic vascular resistance decreases with a concomitant increase in hepatic arterial inflow.

The experimental observations suggest the desirability of continued exploration of the potential usefulness of infusions of Pituitrin in the management of patients with bleeding esophageal varices.

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STUDIES ON THE TREATMENT OF ACUTE RADIATION SICKNESS IN DOGS WITH VARIOUS PREPARATIONS OF SPLEEN

A Preliminary Report

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THERE is good evidence that various preparations of spleen are as effective as bone marrow grafts in the treatment of lethal acute irradiation sickness in small experimental animals (mice, rats, guinea pigs).[1, 5] The evidence is lacking to show that the same is true for the larger experimental animals (monkeys, dogs) which more closely resemble man in their phylogenetic development and/or their sensitivity to irradiation. In the course of transplantation studies in this laboratory, it has been possible to make successful functioning autografts and homografts of the entire small bowel, stomach, or spleen in the dog.[6-8] In the performance of these organ transplants, the technical difficulties of constructing vascular anastomoses between vessels as small as 2 mm. internal diameter have been largely overcome, as evidenced by the fact that dogs with autografts of one or the other of these organs have survived indefinitely despite severance of all lymphatic and nervous connections to the autograft.[3] Since any of these organs apparently can also be preserved in vitro for up to 5 hours without loss of viability when they are once again returned to the host as an autograft, it appeared possible to remove the spleen of a dog and preserve it in vitro while the animal was exposed to lethal total body irradiation. The spleen could then be replaced as an autograft after the irradiation and the ameliorating effect of this procedure on the aftermath of such irradiation could be observed. The failure of this procedure to protect dogs against lethal total body irradiation led to other experiments in which the spleens were shielded in vivo from similar doses of irradiation. We could thus determine whether or not the failure of the whole spleen autografts to protect the dogs was merely the result of the surgical procedure itself. These experiments were in turn compared with results in a third group of dogs in which the spleen was also removed surgically prior to irradiation but was returned afterward to each dog as an intravenous homogenated autograft. This report was prompted by the curious fact that only the intravenous splenic homogenate protected almost all dogs against lethal body irradiation, while the whole spleen autografts or shielding of the spleen did not.

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METHODS AND PROCEDURES

Dogs used in this study were mongrels of both sexes weighing from 10 to 20 kilograms. Because of a lack of confinement space, it was not possible to quarantine dogs prior to an experiment for any specified period of time after their arrival in the kennel. Therefore they could not be dewormed or immunized against canine distemper and hepatitis. The sole method of selection was to use adult dogs in apparent good health in which white blood cell counts were under 15,000 and hematocrits were 40 per cent or above. We had previously determined that dogs in our laboratory rarely survived 300 r given to the total body and all dogs succumbed to 500 r even when treated by forced feedings, parenteral fluids, blood, and parenteral antibiotics.

The irradiation was delivered with a 250 KVP, 30 Ma. unit. The filter was 0.5 mm. Cu; half-value layer, 1.5 mm. Cu; focal skin distance, 120 cm.; and field size, 80 cm. in diameter. The irradiation was delivered at a rate of 22.6 r per minute. The anesthetized dogs were laid on their sides and the irradiation was given through a lateral port with one-half of the total exposure being given to each side. Doses used are stated as "minimum tissue doses" and were calculated at the midsagittal plane of the dog. Therefore, the maximum dose received by any single area varied (according to the thickness of the dog) between 146 and 178 per cent of the stated minimum tissue dose.

Prior to the experiment a bone marrow specimen was obtained for differential count and hematocrit along with a peripheral blood specimen for hematocrit, white blood count, and differential count. The peripheral blood studies were repeated daily after irradiation and the bone marrow was sampled periodically after the irradiation. All dead dogs were autopsied and representative survivors were sacrificed at periods of 1 to 6 months after an experiment. The individual experiments in this study could be classified into 4 groups.

Group 1.—Eighteen control dogs were anesthetized with pentobarbital sodium or thiopental sodium. Four of the dogs were given 300 r, 4 were given 400 r, and 10 were given 500 r to the total body. After irradiation, a careful check on nutrition was made and forced oral feeding and/or parenteral feeding instituted as necessary. In addition, daily antibiotics were given parenterally, usually penicillin and streptomycin. Moreover, in 3 dogs receiving 500 r, neomycin and Sulfasuxidine were started 2 to 3 days prior to the irradiation and were continued afterward to sterilize the bowel and allow us to observe whether or not this had any beneficial effect on survival.

Group 2.—Fifteen dogs which were to receive autografts of the intact spleen were prepared as those in Group 1. Five of these dogs were given neomycin and Sulfasuxidine orally prior to and after the irradiation. These dogs were anesthetized and, with aseptic technique, the spleen was carefully dissected out until it was attached only by the splenic artery and vein. Kapp-Beck clamps (the best vascular clamps for small vessels, in our estimation) were applied to these vessels and they were divided after the spleen had been tightly contracted

with intravenous epinephrine to empty it of blood. After closure of the abdominal incision with a running suture or with towel clips, the dogs were carried to the x-ray therapy room and given 500 r. Meanwhile, the removed spleen was placed in a sterile plastic bag and immersed in a beaker of normal saline cooled to 5° C. Here the spleen was preserved in vitro until the dog was returned. Then the abdominal incision was reopened and the spleen placed in the dog as a total organ autograft by re-establishment of the continuity of the splenic vessels. The vascular anastomoses were carried out with a continuous stitch of No. 6-0 silk. To remove any excess tension on the splenic vessels, we obtained added support by sewing the divided gastrosplenic mesentery back to the greater curvature of the stomach.

In previous experiments in normal unirradiated dogs, we had established that total spleen autografts could be accomplished with consistent success. At exploratory operations at varying intervals up to 6 months after the procedure, the spleen in such dogs was normal in appearance, the splenic vessels were patent, and the spleen contracted promptly when epinephrine was injected systemically.

The irradiated dogs receiving the total spleen autografts were followed in the same manner as the controls.

Group 3.—Eleven dogs which were to receive shielding of the spleen in vivo during total body irradiation were prepared for the irradiation as those in Group 1. They were anesthetized and the abdominal cavity was opened aseptically. The spleen was freed completely by division of the gastrosplenic omentum until it could be easily pulled out to lie on the abdominal wall, even though it was pedicled on the splenic vessels which were still intact. After closure of the abdominal incision around the splenic vessels with the spleen left outside the peritoneal cavity, the dog was carried in a sterile sheet to the x-ray therapy room. There the spleen was enclosed in a lead box and the dog was given 500 r. The spleen received less than 25 r by actual measurement. The dog was then returned to the laboratory where the abdominal incision was reopened, the spleen replaced, and the incision was closed. These dogs were also followed in the manner described for Group 1.

Group 4.—Twelve dogs which were to receive an intravenous autograft of homogenated spleen were prepared as those in Group 1 and anesthetized. With aseptic technique, the abdominal cavity was entered and the spleen removed after it had been tightly contracted with epinephrine injected systemically. The abdominal incision was closed and the dog transported to the therapy room to receive 500 r. While the dog was receiving the irradiation, the removed spleen was sliced into small pieces and passed through successive screens containing 30, 40, 60, and 100 holes per inch.[12] The stroma of the spleen was discarded while the homogenate obtained after passage through the finest screen was diluted up to 150 to 200 ml. with Tis-u-sol* and returned to the dog as an intravenous autograft after completion of the irradiation. No untoward reactions were noted in the dog after the injection of this homogenate which

*Baxter Laboratories.

usually contained from 5 to 9 billion cells, exclusive of red cells, of which 90 to 95 per cent were viable, as seen by the neutral red staining technique used on aliquots of the homogenate. Dogs treated in this manner were also followed in the manner described for Group 1.

RESULTS

In Table I are given the results of these experiments. In no case were dogs counted as survivors unless they had lived at least 4 weeks after an experiment and, in fact, no dog that had survived at least 1 month died at a later date. Dogs which died in all groups were usually dead by the eighth or ninth day after irradiation. The clinical course of dogs in the various groups and the autopsy or sacrifice findings are described below.

TABLE I

GROUP	NO. DOGS	PROCEDURE	DOSAGE OF TOTAL BODY IRRADIATION (r)	NO. SURVIVORS*
1	18	Controls	300-500	1
2	15	Autograft of total spleen	500	1
3	11	Shielding of spleen	500	3
4	12	Autograft of homogenated spleen	500	10

*Survived 4 weeks or longer.

Group 1.—Control dogs receiving 300, 400, or 500 r usually showed the first effect of the irradiation by the third or fourth day. Appetites declined and these dogs usually drank only milk or water, eschewing solid food. By the fifth to sixth day, it was necessary to force-feed the dogs by placing food in the posterior pharynx and to give parenteral fluids and blood. Despite this, all dogs in this group were dead by the ninth day after irradiation with only one exception. This dog had received 300 r and is still alive 1 year later.

The white blood counts of the dogs which died had declined steadily from the fourth day onward until, at the time of death, the count was invariably less than 200 cells per cubic millimeter and in most cases was less than 100 (Fig. 1). The bone marrow biopsies showed an almost complete disappearance of nucleated cells but platelets in the peripheral blood usually remained above 50,000 per cubic millimeter. While stools were often softer than normal, diarrhea was not a problem at this dose of irradiation. At autopsy, the principal findings were hemorrhagic pneumonia and a thin, pale bowel with occasional mucosal hemorrhages. The spleen was small and weighed less than 25 grams in most cases.

Group 2.—All dogs receiving autografts of the intact spleen, with the exception of the first dog in which an autograft was performed, died after the irradiation. Eleven of the dogs died in 9 days or less. At autopsy, the autografted spleen appeared viable and the splenic arterial and venous anastomoses were widely patent. These dogs had the typical hemorrhagic pneumonia characteristic of acute irradiation death. In 1 dog, dead at 5 days, the splenic vein had thrombosed and the spleen was markedly engorged, weighing almost 600 grams. Two other dogs died prior to the seventh day of small bowel

intussusception, a not uncommon nonspecific cause of death in dogs after laparotomy for any reason. The one survivor is still alive in good health 9 months after the irradiation.

The course to death in the 11 dogs which died of acute irradiation sickness in this group was no different than that in controls in Group 1. White cell counts dropped progressively to less than 200 cells per cubic millimeter just prior to death and only an occasional nucleated cell could be seen in the bone marrow at this time. In these dogs, as in the controls, it was necessary to resort to forced feeding and parenteral fluids 4 to 5 days after the irradiation.

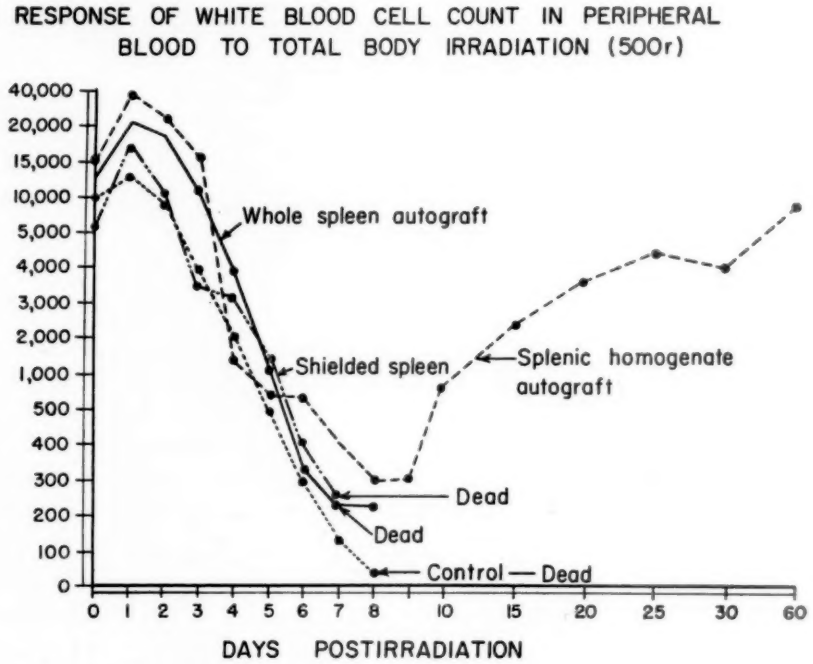

Fig. 1.—Peripheral white blood cell response in typical experiments.

Group 3.—Results with dogs which had shielding of the spleen in vivo during the irradiation were a little better than those seen in Group 2. Five of the dogs showed the typical clinical blood and bone marrow signs of acute irradiation sickness and were dead in less than 9 days. Two more died between 14 and 21 days. One dog died on the sixth day of an intussusception and the 3 remaining dogs were survivors. One of these was sacrificed after 2 months and showed pale, atrophic gastrointestinal mucosa and shrunken mesenteric lymph nodes. The others are being retained for long-term observation.

Group 4.—Dogs receiving an intravenous autograft of homogenated spleen followed a course which was distinctly different from that of dogs in the first 3 groups. Although the peripheral white blood cell counts began their decline at the usual time, they did not drop below 300 per cubic millimeter. By the seventh to tenth day the white counts began to rise and nucleated cells also began to appear in increasing numbers in the bone marrow. The striking finding in these dogs was in their clinical condition after irradiation. Anorexia

did not occur although the appetite for solid foods dropped off somewhat about the seventh or eighth day. In addition, the dogs remained alert and active in their cages. Because of this no parenteral feedings were needed. By 2 weeks after irradiation, these dogs were eating a normal diet and by 3 weeks the peripheral white blood count and the bone marrow had returned to near pre-irradiation levels. All but 2 of these dogs survived the irradiation and the survivors have been sacrificed at varying periods after at least 1 month's survival or are being kept for long-term observation. No late deaths have occurred so far. Few abnormal findings were seen in the sacrificed survivors other than a generalized hypertrophy of the lymphatic tissues, most noticeable in the mesenteric lymph nodes, and a pale, atrophic gastrointestinal mucosa.

DISCUSSION

Investigators have previously reported that mice, rats, and guinea pigs can be protected against lethal total body irradiation by a variety of splenic preparations including homogenates,[5] cell-free extracts, or even the scattering of splenic fragments around the peritoneal cavity, as well as by the shielding of the spleen during irradiation.[1, 4, 5, 11] It is evident from the above results that the same is not entirely true for the dog. The whole spleen autografts afforded no discernible protection to the dogs. The failure of the whole spleen autografts to afford protection was not merely a result of technical difficulties in making anastomoses of small vessels, for these vessels were usually patent in such dogs at autopsy. Furthermore, the failure of shielding of the spleen to afford significant protection also provided indirect evidence that the failure of whole splenic autografts to protect against irradiation was not a result of some technical failure. It should be noted that spleen shielding has also failed to protect rabbits against lethal irradiation.[5]

The question concerning the salutary results obtained with the intravenous autografts of splenic homogenates remains, at present, whether it is the cells from the spleen and/or the noncellular extract of the spleen which is responsible for the favorable outcome in these dogs. Jacobson[5] and Ellinger[1] have both reported that a cell-free extract of spleen will protect rats and mice against lethal irradiation. In the case of the dogs, it appears that the protection may be cellular also since the white cell counts of these dogs did not drop to the low levels seen in controls or in dogs in Groups 2 and 3. Obviously it will be necessary to tag the spleen cells in some manner before reinfusing them into the dogs so that their presence can be recognized in the bone marrow if they, in fact, do help repopulate these vital areas. Wherever the protection provided by the splenic homogenates originates, it appears to be due to some substance which cannot be released by the intact spleen or is not released in significant amounts to afford protection to the lethally irradiated dog. In contrast, maceration and homogenization of the spleen provide striking protection and were found by us to be at least as effective as the bone marrow autografts used to protect against the same dose of irradiation. Ferrebee and associates[2] have reported that up to 4 to 5 billion cells can be obtained from the dog by aspiration of all available marrow sites. Twice this number of cells can usually be

obtained from the spleen. Moreover, if the protection afforded against lethal irradiation is indeed roughly proportional to the number of cells injected,[10] then the value of such large numbers of cells easily obtainable from the spleen is immediately evident. Finally, the protection afforded by the splenic homogenate seems more significant because we have not isolated the irradiated dogs and they have lived in kennels in which they were constantly exposed to a reservoir of infection from new stock dogs continually acquired.

The obvious goal of these experiments is inactivation of the dog's immunologic system so that the various organ homografts can be installed in new hosts with prospects of a prolonged functioning survival. While it appears that the dose of irradiation necessary to inactivate the immunologic systems of small animals is very nearly the same as the lethal dose, in the dog and probably also in human beings, the dose needed to inactivate immunologic activity is, unfortunately, considerably greater than the lethal dose.[9] With this in mind, we are continuing experimentation with combinations of bone marrow and splenic homogenates, as both autografts and homografts, in an effort to salvage dogs after total body irradiation of 1,000 r or more.

SUMMARY

All but 1 of 18 dogs died after total body irradiation of 300 to 500 r minimum tissue dose given in the midsagittal plane. Almost all dogs receiving an autograft of intact spleen after 500 r or having the spleen shielded during irradiation of 500 r also died of irradiation sickness. In contrast, almost all dogs receiving an intravenous homogenate of their own spleen after 500 r survived the irradiation. These findings indicate that homogenization of the spleen releases or makes available substances and/or cells which are not available to the same extent from the intact spleen. Moreover, in our experiments, the homogenized spleen gave protection against lethal total body irradiation equal to that obtained with bone marrow at the same dose of irradiation.

Mr. Don Battles and Mr. James Marquardt, senior medical student, gave inestimable help in carrying out these experiments. Neomycin was furnished as Mycifradin by the Upjohn Company.

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BLOOD VESSEL THROMBOPLASTINS AND EARLY THROMBOSIS AFTER VASCULAR OPERATIONS

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ALEXIS CARREL[5] described a satisfactory technique for end-to-end blood vessel suture in 1902. Four years later he and Guthrie reported the "patching" technique for joining a patch of vessel surrounding the orifice of a small artery or vein to the side of another large vessel.[6] This method reduced the incidence of early thrombosis of small vessel anastomoses and permitted the first renal and ovarian transplants.

In the last few years blood vessel anastomosis, replacement, and repair have become standard surgical procedures. Suture materials, anesthesia, and surgical care in general have improved markedly but the techniques of blood vessel suture are unchanged. Early thrombosis at vascular suture lines remains a problem to surgeons of today as it did to Carrel in the pioneer days.

Clinical and experimental experience has demonstrated that clotting is more likely to take place at suture lines in surgically small, but anatomically medium-sized, or muscular vessels than in large elastic or fibrous ones. The almost axiomatic explanation of this phenomenon has been that mechanical turbulence and/or stasis of blood flow produced by an irregular or narrowed orifice initiates blood coagulation. A standard amount of irregularity produces a more marked effect in small than in large vessels and the small vessels are more prone to early thrombosis than large ones.

An alternative explanation of intravascular thrombosis was proposed by Sawyer[13] who reported finding electric potential differences across injured or cut blood vessels. Because a clot can be produced by passing an electric current through blood, he postulated that the electric potentials from the cut edges of the vessels initiated thrombosis. The electric potential differences across blood vessels were measured under a wide variety of conditions by Eisner and associates.[9] The magnitude of the electric potentials reported by Sawyer could not be confirmed and the physiologic effect of such currents was considered insignificant.

The observation which led us to question the mechanistic explanation of early clotting of vascular anastomoses was clot formation in the inferior pulmonary venous anastomoses of 4 successive dogs with autoreimplanted left lower lobes.[10] In each case a minute area of cut pulmonary venous wall faced into the anastomosis. Pulmonary veins are unusual blood vessels in that they are tubes of muscle lined by endothelium. The thromboplastic effect of cut muscle

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was used for years to obtain hemostasis, particularly in neurosurgical procedures.[7] We believed that the thromboplastins from the muscle of the cut pulmonary vein wall might have caused thrombosis of these anastomoses and we therefore adopted a suture technique which everted the pulmonary venous walls. We had no further difficulty with clotting in the pulmonary vein in subsequent lobe reimplantations.

The following experiments were performed to measure the relative thromboplastic activity of various tissues and blood vessels.

METHODS

Large adult dogs of both sexes were used in these experiments. They were anesthetized with pentobarbital sodium (30 mg. per kilogram) and exsanguinated.

Blood was mixed with 3.1 per cent sodium citrate in a ratio of 10 to 1. The citrated blood samples were centrifuged at 3,000 r.p.m. for 30 minutes to obtain citrated normal plasma.

The femoral arteries and veins, thoracic aorta and venae cavae, pulmonary artery and veins, brain, heart, and lungs were removed by sharp dissection. The vessels were opened longitudinally and washed with saline to free them of blood and clot. Side branches were cut off flush with the main vessel to prevent having a mixture of anatomically different types of vessels. Loose adventitia was trimmed away to the same degree as in the preparation of the vessel ends for an anastomosis.

All tissues were weighed, mixed with 0.85 per cent NaCl (10 c.c. per gram) and homogenized with high-speed tissue blenders. In pilot experiments extracts of vessels which had been ground in a mortar were tested for thromboplastic activity. Reproducible results could not be obtained with different batches of the same vessel. The toughness of blood vessels makes it impossible to obtain a uniform sample by the grinding method. Accordingly we used saline-blended, filtered extracts of the entire vessel in these experiments. When this method of preparation was used, reproducible results were obtained. The 1 to 10 dilution was used to avoid the inhibition of thromboplastic activity seen with high concentrations of tissue extract.[1]

One-stage prothrombin times were determined by mixing 0.1 ml. of citrated plasma and 0.1 ml. of thromboplastin solution in tubes three-eighths inch by 4 inches. The clotting time in seconds was measured after the addition of 0.1 ml. of M/40 $CaCl_2$. All manipulations were carried out in a water bath at 37° C. All clotting times were the average of 4 determinations at each point.

The following experiments were performed:

Group I.—One-stage prothrombin times were measured on 1 to 10 dilutions of the tissues from 6 dogs. The prothrombin time of 1 to 10 abdominal aorta was measured in addition.

Group II.—One-stage prothrombin times were determined with thromboplastin solutions at dilutions of 1 to 10, 1 to 20, 1 to 100, and 1 to 250. These

solutions were prepared by dilution of 1.00 ml. of the 1 to 10 dilution to 2.00, 10.00, and 25.00 ml. in volumetric flasks. This technique was preferred to serial dilution because it prevents multiplication of pipetting errors.

Group III.—Pieces of tissue with an area of 14 cm.^{2} were placed in 50 ml. flasks containing 10 ml. of 0.85 per cent NaCl. These flasks were placed in an incubator at 37° C. and swirled gently every 15 minutes. Dilution curves (Group II) and solubility studies (Group III) were performed on the same vessel to obtain a measure of the physiologic thromboplastic activity of intact rather than homogenized tissues. Equal areas of femoral vein had much more activity than thicker, heavier pulmonary artery or thoracic aorta. The comparison of the tissues by surface area was thus more valid than comparison by weight or thickness. Samples of saline were withdrawn at intervals for determinations of the one-stage prothrombin time.

RESULTS

Group I.—The results of the experiments in Group I are shown in Table I.

These results are the averages of 4 determinations for each tissue from 6 dogs. Because blood coagulation is a relatively slow, multistage chemical reaction the spread of values was appreciable. When this was analyzed statistically, however, the variance for the determinations on each tissue was remarkably constant.

TABLE I. THROMBOPLASTIC ACTIVITY OF TISSUE EXTRACTS AT 1 TO 10 DILUTION

TISSUE	CLOTTING TIME (SEC.)	% BRAIN ACTIVITY
Brain	16.4	100
Lung	16.9	90
Heart	32.2	10
Femoral vein	33.3	10
Femoral artery	33.6	10
Pulmonary vein	33.8	10
Pulmonary artery	44.7	6
Thoracic aorta	48.7	5
Abdominal aorta	51.7	4
Thoracic vena cava	55.9	3
Saline	110.0	0.1

The slopes of the thromboplastin dilution curves for the various tissues differ and thus their relative activity holds only at this one dilution. Although the exact relationship varies slightly with concentration, moderate concentrations of homogenized brain are approximately 10 times as active as heart, femoral artery and vein, and pulmonary vein. Brain was approximately 50 times more active than pulmonary artery, thoracic aorta, or thoracic vena cava (Fig. 1).

The clinical practice of reporting prothrombin times as percentage of prothrombin activity and considering values of less than 10 per cent as an anticoagulant level is misleading. Although patients may bleed abnormally at less than 10 per cent levels, there is appreciable thromboplastic activity of brain extracts at a 0.01 per cent concentration. The validity of this concept is

illustrated by the necessity for use of statistical methods to demonstrate clinical benefit to patients receiving anticoagulant therapy.

Although striking differences exist between the relative thromboplastic activities of the 3 groups of tissues analyzed in Group I, they all possess considerable thromboplastic activity.

Group II.—Determinations of one-stage prothrombin time on similar dilutions of heart, femoral artery and vein, and pulmonary vein gave parallel slopes when their logarithms were plotted against the logarithms of their concentrations. A set of parallel curves of different slope was obtained for pulmonary artery, thoracic aorta, and brain. Curves of different slopes were also seen for thoracic vena cava and for lung. These are illustrated in Fig. 2.

The implication from these curves is that the thromboplastic substance from vessels with parallel dilution curves is the same.

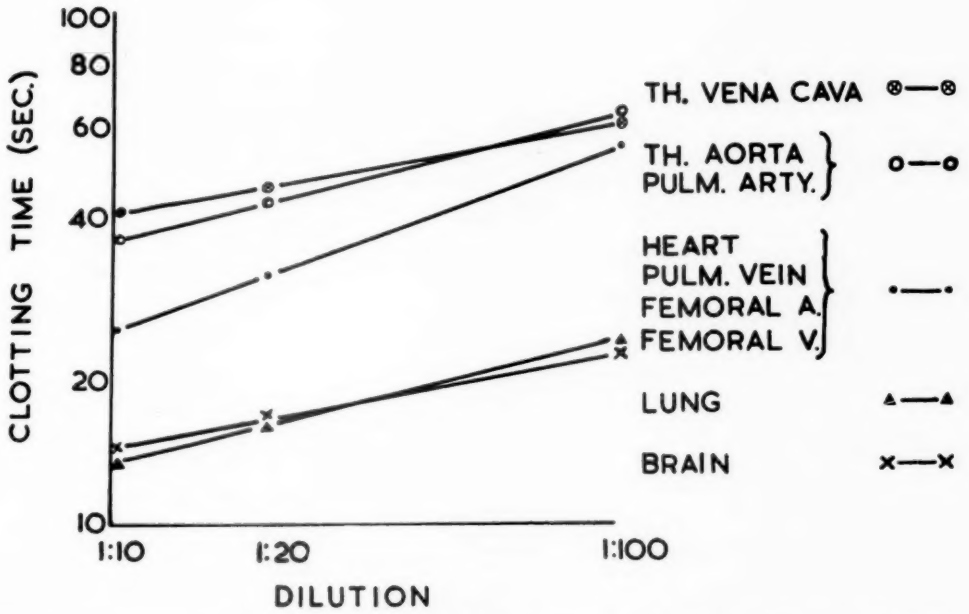

Fig. 1.—One-stage prothrombin times with use of 1 to 10 saline extracts of various tissues.

The similarity of heart, femoral artery and vein, and pulmonary vein is presumably related to the muscle of their walls. The elastic vessels (pulmonary artery and thoracic aorta) and brain behave similarly. The similarity between the members of each group has been analyzed statistically and there is a value of $P < 0.001$ for the muscular group and $P < 0.02$ for the elastic group and brain.

Group III.—Comparison of thromboplastic activity of homogenized extracts of tissues does not give a measure of the solubility of thromboplastins under physiologic conditions. Samples of saline in which pieces of heart, pulmonary vein, and femoral artery and vein had soaked had an activity equivalent to a 1 to 100 extract of homogenized vessel at the end of 15 minutes. The pulmonary

artery and thoracic aorta had activities equivalent to 1 to 2,000 dilutions of the homogenized vessel. Thoracic vena cava had a 1 to 200 equivalent activity.

The actual numerical values obtained in the solubility studies are meaningless, but the relative solubility is valid.

If one multiplies the relative activity of the various groups by the relative solubility of whole vessels, a measure of the relative physiologic thromboplastic activity is obtained. This is shown in Table II.

TABLE II. RELATIVE PHYSIOLOGIC THROMBOPLASTIC ACTIVITY OF BLOOD VESSELS

VESSEL TYPE	RELATIVE ACTIVITY		RELATIVE SOLUBILITY		RELATIVE THROMBOPLASTIC ACTIVITY
Muscular	2	×	20	=	40
Fibrous	1	×	10	=	10
Elastic	1	×	1	=	1

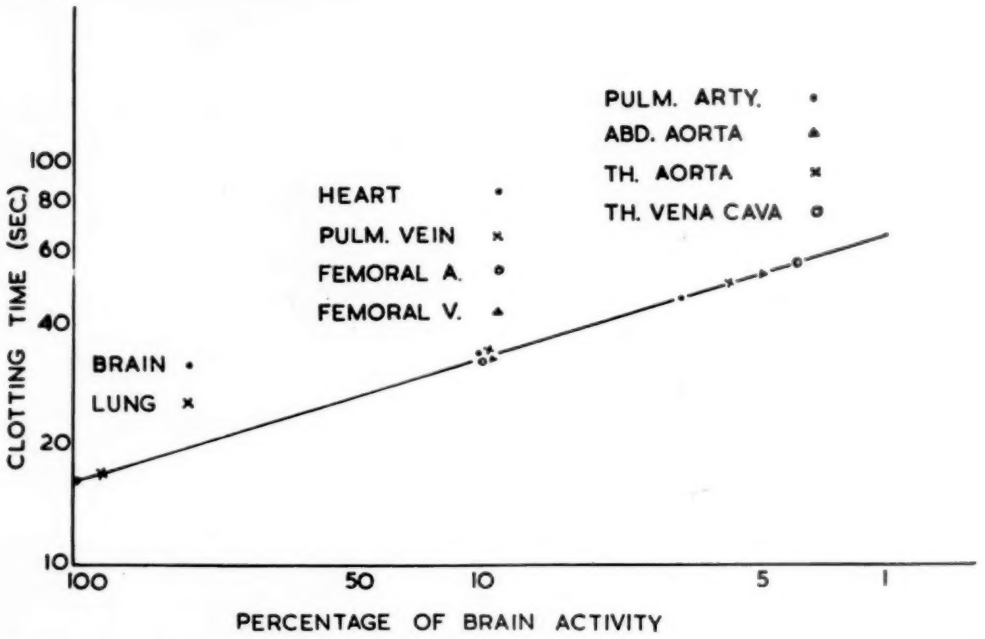

Fig. 2.—Thromboplastin dilution curves demonstrating differences in slope for different groups.

DISCUSSION

The concept of vessel size as the factor which controls the tendency of vascular anastomoses to thrombose leaves many observations unexplained.

Blood can pass and regurgitate for years through stenotic and often irregular mitral valves. There is turbulence distally and stasis proximally, but, unless coordinated contractions cease in the atrium, intracardiac thrombosis is uncommon. The Korotkoff sounds heard when one measures blood pressure by the cuff method are the result of turbulence produced by blood squirting through the compressed brachial artery. There is stasis proximally and turbulence distally, but thrombosis in the arm is not a common hazard of blood pressure measurement. An intoxicated person can rest his arm over the back of a bench

long enough to produce "gin drinker's palsy" from radial nerve damage, but gangrene from concomitant brachial artery compression is unknown.

In each of these situations a substantial amount of turbulence exists, but thrombosis does not take place. There are also numerous situations in which varying degrees of pure stasis are present without intravascular clotting.

Patients under anesthesia may lie for hours strapped in one position on the operating table without great danger of thrombosis. Tourniquets are frequently applied to obtain a bloodless field for operations on extremities. If these are applied for a prolonged period the surgeon may be concerned about ischemic damage, but not thrombosis. Soldiers on parade may worry about fainting from standing motionless, but they do not worry about thrombosis. When kidneys are being transplanted, they are without active circulation for several minutes. To use anticoagulants during such procedures is neither necessary nor desirable.[12] A reduced rate of blood flow may be tolerated for long periods without danger of clotting.

An endarterectomy, anastomosis, or graft in a vessel with an unrelieved distal block is likely to thrombose. This is most commonly seen in patients with femoral arterial reconstructive procedures and poor "run-off" in the lower legs. In this situation there is little mechanical turbulence by virtue of the reduced, but not necessarily absent, blood flow. This clinical observation is strong evidence pointing to the importance of a local tissue factor in early thrombosis.

Additional support for the importance of a local factor is the tendency of pulmonary venous anastomoses to thrombose if they are joined by techniques which are suitable for other vessels of comparable size. In our series there was a definite propensity to clot when the veins were sutured with an over-and-over stitch. This was prevented by an exact everting anastomotic technique.

Borrie and Montgomerie[3] reported death of 6 of 10 sheep with autoreimplanted lungs from thrombosis of the pulmonary vessels and congested necrosis of the transplant. The bronchial vessels are completely divided when one removes and replaces a lung. If the pulmonary vessels subsequently become occluded the lung undergoes necrosis and is congested or anemic, depending on whether the vein or artery becomes thrombosed first. It is likely that the primary event with the animals of these authors was pulmonary vein thrombosis.

Davis and colleagues[8] reported thrombosis of the superior pulmonary vein as the cause of death of 1 of the 5 dogs in which they completed the operation of lung homotransplantation. This occurred despite postoperative heparinization to a level which caused death of 3 of the 5 from hemorrhage.

Juvenelle and associates[11] reported many attempts at excision and reimplantation of the right lung of dogs before a long-term survivor was obtained. Because the results of pulmonary artery and bronchial suture are generally quite satisfactory, this would appear to point to difficulty with the pulmonary venous anastomosis.

Although a tendency for pulmonary venous anastomoses to thrombose has not been reported in the literature as such, it would appear that the problem

does exist and has been experienced, but not noted. Pulmonary veins are large vessels and would not be expected to thrombose according to the vessel size-turbulence-stasis theory. Their tendency to coagulation points to the action of a local factor initiating clotting. The physiologic thromboplastic activity of pulmonary veins is high.

The converse situation is seen in the case of shunt operations for tetralogy of Fallot. In these patients there is a markedly increased tendency of the blood to clot, but thrombosis of aortic or subclavian to pulmonary artery anastomoses is not common. This would indicate minimal activity of tissue factors in this instance. The physiologic thromboplastic activity of elastic vessels is low.

Considered in its entirety, blood clotting is an all or none phenomenon—blood is either liquid or clotted. The speed of blood coagulation is modified by the presence and concentration of many factors.

It is the general desire of surgeons that patients undergoing operation should have a normal clotting mechanism. If this is the case the problem is simplified and coagulation may be thought of in terms of the classical two-stage theory:

I. Prothrombin + thromboplastin + Ca → thrombin
II. Thrombin + fibrinogen → fibrin

Any substance which speeds coagulation of recalcified normal plasma is considered to have thromboplastic activity.[2] The addition of thromboplastin is all that is required to initiate coagulation.

The amount of clot formed in vivo is regulated by the rate of inactivation of thrombin by antithrombins and absorption on fibrin and by the lysis of formed clot by fibrinolysins. For gross blood coagulation to take place the thromboplastin concentration must reach a critical level. In the case of vascular anastomoses this is determined largely by the physiologic nature of the vessels being sewed. Muscular vessels readily liberate a strong thromboplastic substance. Elastic vessels liberate a different weaker substance in lower concentration. Fibrous vessels are between elastic and muscular vessels in thromboplastic activity.

Campbell[4] analyzed ground bovine thoracic aorta for thromboplastins and reported it to be an active thromboplastic substance. However, the concentrations he used were much greater than those used in our experiments. Extrapolation of our dilution curves for brain and thoracic aorta to the concentrations he used gives clotting times and relative activities of brain and thoracic aorta of the same order of magnitude found in his experiments. In addition, Campbell dissected his aortas into intima, media, and adventitia and performed prothrombin times on each component. The highest activity was in the adventitia. This discovery correlates well with surgical experience that adventitia drawn by a needle into an anastomosis is likely to cause early thrombosis.

From the above discussion it is clear that there are serious inadequacies in the theory that vessel size, stasis, and turbulence control early coagulation of vascular suture lines, anastomoses, and endarterectomies. There are numerous observations which indicate the importance of a local tissue factor. These

observations together with the experiments reported in this paper lend support to a theory which explains observed facts more exactly than does the conventional mechanistic theory.

The factor which determines whether or not thrombosis will take place adjacent to an injured or cut vessel is the local thromboplastin concentration. The thromboplastic substance arises from the wall of the blood vessel, with muscular vessels liberating a large amount, fibrous vessels an intermediate amount, and elastic vessels a small amount. The actual concentration of thromboplastin which develops is the resultant of the rate of liberation and the rate of dilution and removal by the blood stream.

Small vessels, the anastomoses of which tend to thrombose readily, are of different histologic and physiologic type than large vessels in which anastomoses are less likely to clot. The only notable exceptions to the rule of size are the large pulmonary veins which are physiologically and surgically like small vessels.

Stasis acts to promote thrombosis by decreasing the rate of removal of thromboplastins. This applies whether the stasis is general, as in the case of an anastomosis in a vessel with an unrelieved distal block, or local, as in the case of pockets or wrinkling from marked size discrepancy between 2 vessels or inaccurate suture technique.

The object of an anastomosis of intima to intima in small vessels and pulmonary veins is to diminish the amount of thromboplastin liberated into the blood stream and reduce local stasis rather than merely to provide a mechanically smooth anastomosis.

Contractility is an important function which helps to decrease stasis of blood in the heart and prevent local stasis about cardiac suture lines. Intracardiac thrombosis is seen only in conditions in which contractility is abolished either locally, as under a myocardial infarct, or generally, as in auricular fibrillation.

SUMMARY

The brain, lungs, heart, femoral arteries and veins, pulmonary artery and veins, thoracic aorta, and venae cavae of dogs have been analyzed for thromboplastic activity. At a 1 to 10 dilution with saline, homogenized extracts of brain and lung are approximately 10 times more active than heart, femoral artery and vein, and pulmonary vein, and 50 times more active than pulmonary artery, thoracic aorta, and vena cava.

The slopes of the dilution curves of heart, pulmonary vein, and femoral artery and vein are parallel as are the slopes of pulmonary artery, thoracic aorta, and brain. Each of these groups, however, is different from the other and different from lung and thoracic vena cava. The parallel slopes of the dilution curves of the members of the muscular and elastic vessel groups, respectively, imply that the thromboplastic substance within each group is similar and that that in the 2 groups is different.

The solubility of thromboplastic substances from intact muscular vessels was 20 to 40 times greater than from elastic vessels. The physiologic thromboplastic activity of muscular vessels is thus 100 to 200 times that of elastic vessels.

It is proposed that the local thromboplastin concentration is the important factor determining the immediate success of vascular suture, anastomosis, graft, or endarterectomy rather than mechanical considerations based on vessel size.

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THROMBOANGIITIS OBLITERANS IN WOMEN

Report of Two Cases

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SINCE 1908, when Buerger[3] first classified the disease entity which bears his name, there have been hundreds of cases reported in the literature. The majority of these have occurred in males. More than 60 cases occurring in females† have been reported. Of these, only 15 have been presented with pathologic material. In the last year we have encountered 2 pathologically proved cases of thromboangiitis obliterans in women. In view of the rarity of this disease in women these cases are being presented along with some of the controversial points concerning this entity.

CASE REPORTS

Case 1.—A 36-year-old white housewife was admitted to this institution for the investigation of vascular insufficiency of the left foot and leg. One year prior to admission she had developed painful swelling of the left wrist with blanching, cyanosis, and hypesthesia of the hand and fingers. This persisted for 1 week but disappeared with steroid therapy. Three months later she noted the onset of progressive intermittent claudication of the left anterior thigh, the calf, and foot. Four months after this a left lumbar sympathectomy was performed with relief of the rest pain which had been present for 1 month. Subsequently, walking with the aid of crutches caused intermittent claudication of the right foot. One and one-half months prior to admission an ulcer of the fourth left toe appeared and the typical rest pain of vascular insufficiency recurred. There was no history of phlebitis, vasomotor instability, or allergy. She had smoked one-half package of cigarettes a day for 15 years.

The family history showed that a sister had had a leg amputation at 28 and a finger amputation 1 or 2 years later. Microscopic sections of these specimens were not obtainable and we were unable to examine the sister. Her physician, however, stated that the correct pathologic diagnosis was thromboangiitis obliterans. The father and 2 uncles had diabetes mellitus.

Physical examination revealed several positive points. The patient appeared somewhat older than her stated age of 36. She was in severe distress from pain in the left foot. There was minimal enlargement of the right lobe of the thyroid without an audible bruit. There were no occular signs of thyrotoxicosis. The skin was warm and dry and the hair fine. On examination the heart was normal except for a tachycardia of 120. The blood pressure was 120/66 and the palpable pulses were collapsing in quality. There was a positive Allen's sign on the left. The carotid, brachial, radial and right ulnar pulses were palpable and of good volume. The left ulnar pulse was absent. Both femoral and right popliteal

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*Trainee of the National Cancer Institute.

†References to reports of cases in women thought to be thromboangiitis obliterans on clinical grounds but without pathologic study are, for the sake of brevity, omitted.

pulses were present and of good volume. The left popliteal pulse was present but reduced in volume. Neither dorsal pedal nor posterior tibial pulses were present. There were no trophic changes in the hands or right foot, but there was edema, rubor, and hyperesthesia of the left foot. There was an ulcer 1 cm. in diameter with a necrotic base over the lateral aspect of the left fourth toe.

The hemoglobin was 14.3 Gm., the hematocrit 43 per cent, the leukocyte count 15,700 with bands 1 per cent, neutrophils 50 per cent, lymphocytes 38 per cent, monocytes 7 per cent, and eosinophils 4 per cent. The corrected sedimentation rate was 32. The serum cholesterol was 123 mg. per cent. The serum protein was 6.15 Gm. with 4.64 Gm. of albumin and 1.51 Gm. of globulin. The blood sugar and blood urea nitrogen determinations and urinalysis were within normal limits. The protein-bound iodine was 13 γ per cent. The basal metabolic rate was +46 per cent. The L. E. cell preparations were negative on 3 occasions. The serologic test for syphilis was negative. The chest x-ray study was normal. The electrocardiogram showed sinus tachycardia but was otherwise normal. Radioactive iodine uptake studies were in the hyperthyroid range.

Fig. 1.—Left femoral arteriogram of the first patient demonstrating obliteration of the distal arterial tree with smooth but narrowed collateral vessels.

A diagnosis of hyperthyroidism was made in addition to that of vascular disease, and the patient was prepared for operation with methimazole and Lugol's solution. A femoral arteriogram was performed that demonstrated narrowing of the lower two-thirds of the femoral artery and popliteal artery with opacification of only the anterior tibial artery below this. There was no intimal irregularity or segmental obstruction demonstrated (Fig. 1). Because of the poor distal arterial tree, a bypass procedure could not be performed and since a lumbar sympathectomy had already been performed, a leg amputation was carried out. The postoperative course was uneventful and the patient was discharged and put on methimazole for her hyperthyroidism. She has done well to the present time.

Pathologic examination of the amputated left lower extremity revealed it to be grossly discolored. The arteries were thickened and the lumena were distinctly narrowed. The arteries, veins, and nerves were invested in fibrous mantle (Fig. 2). Segmental obliterations of the lumen of the anterior and posterior tibial arteries were noted. Microscopically the internal elastic lamina of both arteries was folded. The lumen of the arteries was occluded by an organized thrombus which showed canalization and a sparse lymphocytic infiltrate.

Fig. 2.

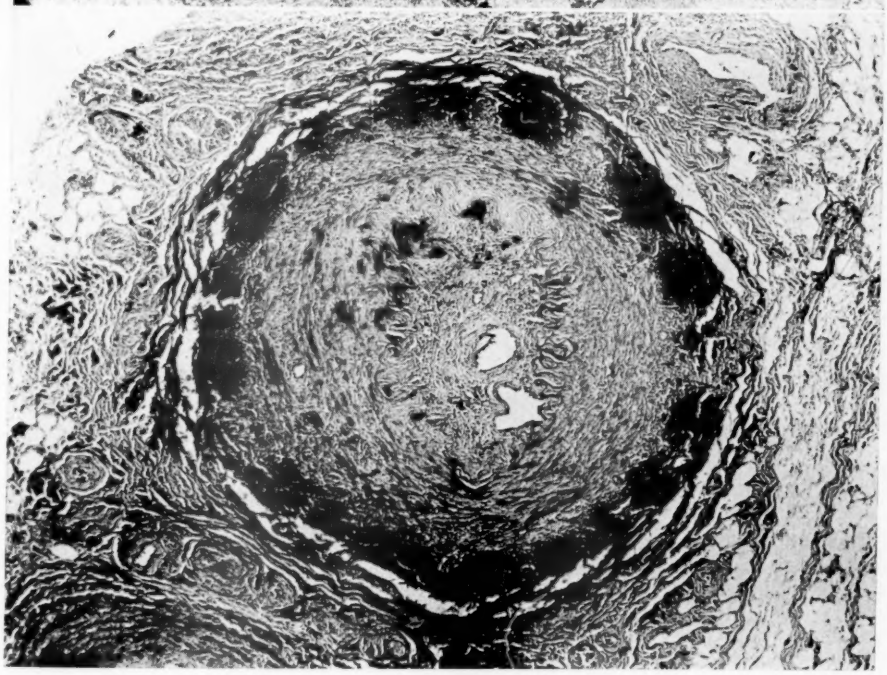

Fig. 3.

Fig. 2.—Posterior tibial artery and vein. Periarterial fibrosis and occlusion of the lumen of the artery are evident. (Hematoxylin and eosin. ×75; reduced ⅓.)

Fig. 3.—Posterior tibial artery. The occlusion of lumen of the artery with recanalization, the periarterial reaction, and the folded and frayed internal elastic membrane are demonstrated. (Verhoeff's elastic stain. ×150; reduced ⅓.)

The wall of the greater saphenous vein was slightly thickened. Focal lymphocytic infiltrates of the adventitia and perivascular connective tissue were noted (Fig. 3).

CASE 2.—A 25-year-old white woman was admitted for investigation of intermittent claudication of the right foot of 1 year's duration. Six months prior to admission the patient had sustained a laceration of the lateral fifth metatarsal region of the right foot. This failed to heal and a painful chronic ulcer developed. Four months later the patient struck her right great toe which became gangrenous and ulcerated. During the previous month she had noted the typical rest pain of vascular insufficiency. Fifteen months prior to admission, after the birth of her child, she developed superficial phlebitis of both calves which subsequently disappeared. She had smoked 1½ packages of cigarettes a day for many years. There was no history of allergy, vasomotor instability, or diabetes. The family history was noncontributory.

Physical examination showed several positive features. The patient was a thin, pale, white woman who appeared chronically ill. The blood pressure was 122/80. Both feet were cool. The right foot was painful and cyanotic with dependent rubor and poor venous filling.

Fig. 4.—Right femoral arteriogram of the second patient demonstrating tapered obliteration with a smooth vascular lumen.

There were trophic skin and nail changes. There was a necrotic ulcer 2 cm. in diameter over the right fifth metatarsal laterally and gangrene of the distal portion of the right great toe. Both femoral arterial pulses were of adequate volume. The left popliteal pulse was present but diminished. Neither the right popliteal nor either dorsal pedal or posterior tibial pulse was palpable.

The hemoglobin was 11.9 Gm. The hematocrit was 37 per cent. The leukocyte count was 12,850 with 5 per cent bands, 81 per cent neutrophils, 10 per cent lymphocytes, and 4 per cent monocytes. The urinalysis, serum cholesterol, and fasting blood sugar were normal. The serologic test for syphilis was negative. The electrocardiogram was normal.

A right femoral arteriogram was performed. It demonstrated obstruction of the superficial femoral and popliteal arteries. The femoral artery was smooth but narrowed in character. The posterior tibial and peroneal arteries were partially opacified by means of a narrow collateral vessel (Fig. 4). After the femoral arteriogram a right leg amputation and left lumbar sympathectomy were performed. The patient had an uneventful convalescence and is doing well.

Fig. 5.

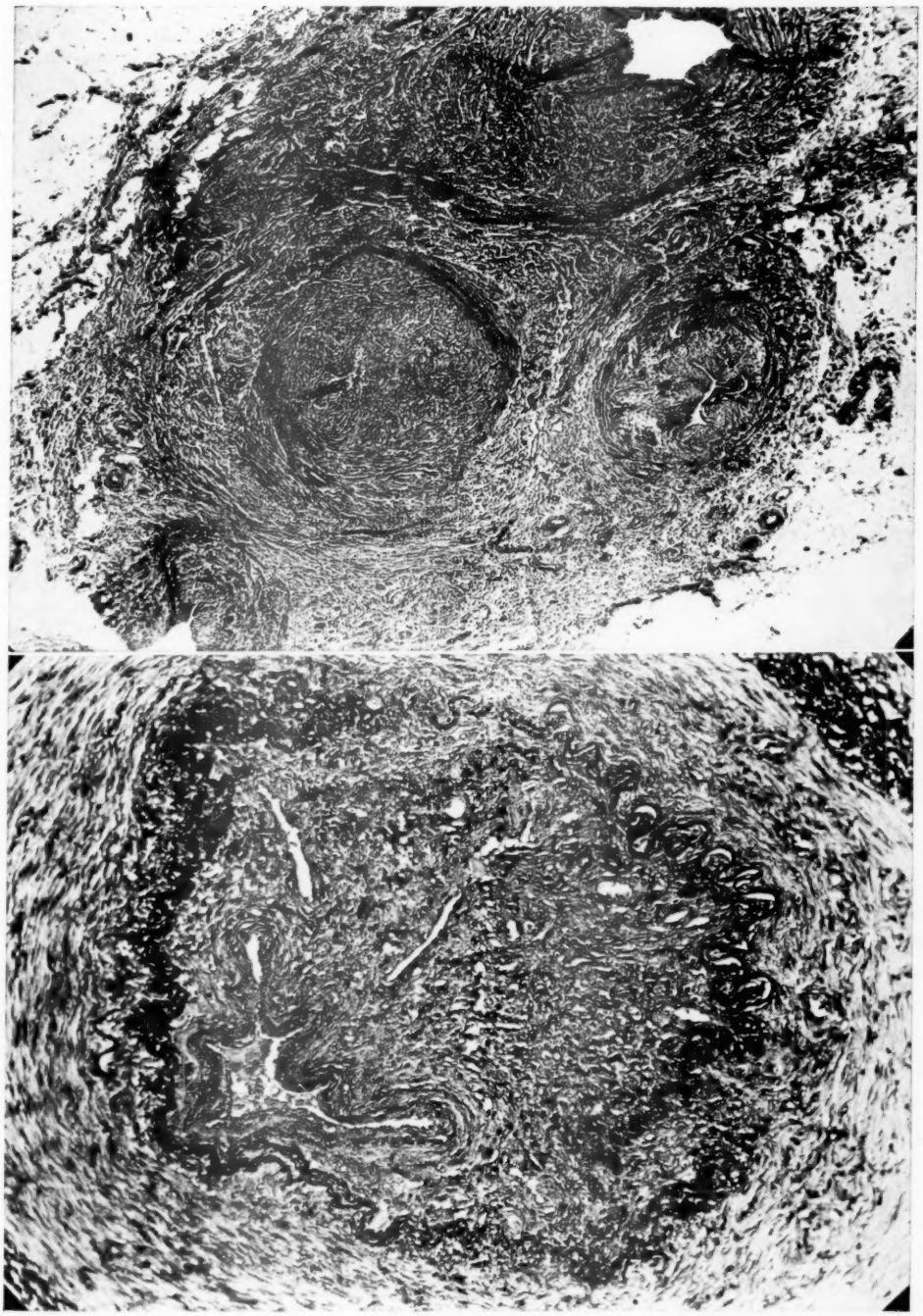

Fig. 6.

Fig. 5.—Distal posterior tibial artery, branch, and vein. There is marked fibrosis binding together the artery and vein. The lumen of the artery is occluded. (Hematoxylin and eosin. ×75; reduced ⅓.)

Fig. 6.—Anterior tibial artery. The lumen is occluded by a partially organized thrombus. A few lymphocytes are noted. The internal elastic lamina is folded. (Verhoeff's elastic stain. ×150; reduced ⅓.)

Pathologic examination of the amputated extremity revealed the soft tissues of the great toe to be necrotic. An occasional ulceration of the skin was noted. Segmental obliteration of the lumen of the anterior and posterior tibial artery was noted. Grossly and microscopically there was present a periarterial fibrosis which bound together the artery, vein, and nerve (Fig. 5). The internal elastic lamina was folded. The lumina of both the anterior and posterior tibial arteries were occluded by an organized thrombus which showed canalization and a sparse lymphocytic infiltrate. A few lymphocytes were noted in the adventitial layer of the arteries (Fig. 6).

DISCUSSION

The clinical diagnosis of thromboangiitis obliterans is generally easily made in typical cases. Quite often, however, the diagnosis is unclear, especially in early cases. It is primarily a diagnosis of exclusion and should be entertained particularly in the absence of any condition which might be the cause of vascular insufficiency such as arteriosclerosis, lipemia, diabetes mellitus, collagen vascular disease, hypertension, changes in hematologic cellular elements, serologic evidence of syphilis, and allergy. There are several conditions which, when present, are helpful in substantiating the diagnosis of thromboangiitis obliterans: (1) the appearance of pertinent symptomatology in an adult before the age of 40, (2) the involvement of peripheral vessels with sequelae of vascular insufficiency such as gangrene, pain, rubor, and ulcers and, if no sequelae are present, the demonstration of an occluded vessel, (3) the occurrence of disease in both upper and lower extremities, (4) the presence or history of superficial thrombophlebitis, (5) the demonstration of the accelerating effect of the use of tobacco on the disease process.

Histologic proof of the lesion affords confirmation of the diagnosis, but often this is difficult to obtain. Relatively innocuous procedures such as skin and muscle biopsy are usually nonproductive from the standpoint of contributing positive pathologic evidence. Examination of amputated specimens, while usually confirmatory, is of limited value because of the relatively low amputation rate, especially early in the course of the disease.

Arteriography may prove to be helpful in delineating the true etiology of suspected thromboangiitis obliterans. In arteriosclerosis obliterans one is usually able to demonstrate vascular occlusion of the segmental variety with intimal irregularity in the patent portions of the vessels. In thromboangiitis obliterans, however, the patent vessel is reported to be smooth and the obstruction tapered. In recent studies this tapered obstruction has been felt to be secondary to recanalization of an old thrombus.[9] The femoral arteriograms of the patients discussed demonstrate arteriographic pictures compatible with thromboangiitis obliterans.

Buerger[3] originally believed that this was a definite disease entity consisting of 3 phases, (1) an acute occlusive thrombosis associated with the formation of miliary giant cell foci, (2) the stage of organization characterized by disappearance of miliary giant cell foci, the organization and canalization of a clot, and the disappearance of the inflammatory products, (3) the development of a fibrotic envelope which encompasses artery, nerve, and vein. Buerger's later concepts placed greater emphasis on the accompanying inflammatory

features.[2] However, Gore[8] as well as Freiman[14] conclude that these lesions are not specific, but are the result of primary intravascular thrombosis. In general, however, they are considered diagnostic of thromboangiitis obliterans. In our opinion our 2 cases are indeed instances of the entity described by Buerger.

Thromboangiitis obliterans is very rare in females. There have been more than 60 cases reported in the literature but very few with pathologic confirmation. In view of the fact that other disease entities such as arteriosclerosis, collagen vascular disease, or nonspecific obliterative arteritis may be confused with true thromboangiitis obliterans, pathologic demonstration of the lesion would be desirable. Admittedly, this is difficult to obtain in most instances. We have found 15 cases of thromboangiitis obliterans in women in which there has been some attempt at microscope verification,[1, 4-7, 10-13, 15, 16] Ten of these cases either have sufficient description, photomicrographs, or both, to warrant their classification as proved instances of thromboangiitis obliterans in women. The 5 remaining cases are probably thromboangiitis obliterans, but we consider the documentation insufficient (Table I).

TABLE I

AUTHOR	YEAR	NO. OF CASES	COMMENT
Atlas	1943	1	Proved
Poteete and Lynch	1956	2	Proved
Horton and Brown	1932	3	Proved
Davis and King	1947	1	Proved
Fisher, Zukerman, and Sweeney	1951	1	Proved
Messent	1954	1	Proved
Meleney and Miller	1957	1	Proved
Gaylis	1957	1	Insufficient documentation
Selvaag	1953	2	Insufficient documentation
Frank	1952	1	Insufficient documentation
Hughes	1949	1	Insufficient documentation

SUMMARY

In the past year we have treated 2 young women whom we consider to have the clinical and pathologic criteria for the diagnosis of thromboangiitis obliterans. Their case histories have been presented, together with some of the clinical, pathologic, and radiographic features of this disease.

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IDIOPATHIC MIGRATORY THROMBOPHLEBITIS

Report of 4 Cases

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MIGRATORY thrombophlebitis often occurs in thromboangiitis obliterans and in neoplasia, particularly visceral carcinoma. The term "idiopathic" should be applied only to those cases in which no cause is found. The young man who smokes and develops superficial thrombophlebitis extending from one vein to another, neither extensively nor rapidly, should be warned conscientiously of the likelihood of his developing Buerger's disease even before arteries have become involved. Biopsy of an involved vein would often show the characteristic intraluminal granuloma. When multiple, rapidly migrating, and recurrent thrombophlebitis appears in people near or past the age of 50, visceral carcinoma should be searched for thoroughly. Recourse to exploratory laparotomy is mandatory even in the presence of all negative results from diagnostic procedures.

Edwards[4] reviewed 23 reported cases of migrating phlebitis associated with carcinoma and added 7 more. Wright[11] reported having found cancer in 20 patients in whom it had been unsuspected until the significance of migratory or persistent thrombophlebitis, despite adequate anticoagulant therapy or unexplained bleeding with therapeutic prothrombin levels, was recognized. Hubay and Holden[5] have contributed 7 additional cases associated with neoplasm, 2 of which were benign, and 1 case associated with infection. We add 4 more, the first 2 through the courtesy of Drs. F. Hernández Morales and E. J. Marchand. The body or tail of the pancreas continues to be the most frequent primary site of malignancy in these cases,[3] about 45 per cent.

CASE REPORTS

Case 1.—P. H. R., a 52-year-old white housewife, developed thrombophlebitis in a superficial varicosed vein on the lateral aspect of the left thigh. The condition responded satisfactorily to bed rest at home. Seven weeks later, the woman suffered a similar process on the medial aspect of the right thigh and upper portion of the leg. This flared up again 10 days later just before an exploratory laparotomy on Sept. 3, 1953, for a palpable, nodular, firm mass in the right upper quadrant which had become evident just 3 weeks previously and which was associated with generalized abdominal discomfort, low grade fever, and 15-pound weight loss. Operation revealed ovarian papillary cystadenocarcinoma with peritoneal implants and liver metastases.

Two weeks postoperatively, the patient developed a typical iliofemoral thrombophlebitis with massive edema of the right lower extremity and pulmonary emboli despite apparently adequate Dicumarol anticoagulant therapy. Six weeks postoperatively she died, presumably of liver failure.

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CASE 2.—J. J. S., a 53-year-old white widow, first developed superficial thrombophlebitis in the pretibial area of the right leg in mid-July, 1953. She was treated with bed rest, elevation, and hot packs. Two weeks later, the process flared up in the posteromedial aspect of the left thigh, this time with a palpable 12 cm. thrombosed superficial vein. She was hospitalized and given Dicumarol for 2 weeks.

Two months later a similar process recurred on the anteromedial aspect at the level of the right knee extending onto the thigh. The woman was rehospitalized for 21 days and treated with Dicumarol anticoagulant. Gastrointestinal series, barium enema, and intravenous pyelography gave negative results. Doubly intensified cholecystography failed to visualize the gall bladder. The history of recurrent gall bladder colic since 9 years previously (the last attack about 1 year from this admission, at which time cholecystography had revealed multiple calculi) together with a palpable liver edge, slight tenderness in the gall bladder area, and nonvisualization at this time indicated the desirability of exploratory operation.

Laparotomy performed at Graduate Hospital, Philadelphia, on Oct. 29, 1953, at the insistent request of the internist, revealed widespread intra-abdominal adenocarcinoma with metastases into the omentum and liver. The primary lesion was probably in the gall bladder or body or tail of the pancreas.

The patient was continued on anticoagulant therapy until death supervened 6 months after the first thrombophlebitic process had occurred.

Edwards[4] is convinced that exploratory laparotomy should be performed even though he is rather pessimistic when neoplasm is encountered. Hubay and Holden[5] concur with this opinion but disagree regarding the prognosis since in many cases the underlying disease may prove to be nonmalignant in character. They further state that if neoplasm is found it should be treated in the same manner as cancer elsewhere. Wright[11] admits that he is now becoming more inclined toward exploratory laparotomy in the presence of persistent phlebitis with negative x-ray and blood studies.

The next case illustrates the difficulties that may be encountered in the differential diagnosis. Had the correct diagnosis been made earlier, the surgical exploration would not have been resorted to. Death supervened 6 months after the initial superficial thrombophlebitis.

CASE 3.—G. T. C., a 36-year-old white housewife, mother of 4, was first admitted on May 27, 1955, with history of superficial thrombophlebitis on the ulnar aspect of the entire right arm, forearm, and hand of 3 weeks' duration and similar induration along the internal saphenous vein in the lower third of the right leg of 2 days' duration. She was discharged improved 5 days later to continue treatment at home. She was admitted to another hospital for evaluation, regarding an occupational claim, on June 16, 1955, and was discharged 3 days later despite sudden severe right chest pain and dyspnea, pain in extremities with signs of local recurrent thrombophlebitis, and fever of 2 days' duration for which she was readmitted here on June 20.

The readmission clinical diagnoses were acute deep thrombophlebitis in the left calf, persisting superficial thrombophlebitis of the right upper extremity, and acute pulmonary embolism. Despite anticoagulant Dicumarol therapy, patient developed signs of deep thrombophlebitis of the right leg on the third hospital day and on the tenth, classic right ileofemoral thrombophlebitis with massive swelling of the entire right lower extremity, although then the prothrombin level was 40.1 seconds (control 13.8 seconds) and it reached 68 and 58.4 seconds in subsequent days. On August 1, Tromexan was gradually substituted for Dicumarol and massive, bilateral, continuous warm saline compresses and elevation were instituted. With prothrombin levels of 26 to 32 seconds, the patient developed superficial thrombophlebitis on the right lower extremity and recurrent deep thrombophlebitis in the left leg.

Because of the acute illness, exclusion of malignancy by diagnostic survey had not been possible except for chest x-ray studies and gastrointestinal series, July 21, 1955, which were negative for pulmonary infarct and malignancy.

On June 21, 1955, the hemogram was hemoglobin 100 per cent (14.5 Gm.), red blood cells 4.5 million, color index 1.1, white blood cells 4,450, segmented cells 55, lymphocytes 43,

eosinophils 2, and sedimentation rate 43 mm. per hour. On June 24, platelets were 131,000. On June 28, the hemogram was hemoglobin 83 per cent (12.1 Gm.), red blood cells 3.8 million, color index 1.0, white blood cells 4,750, segmented cells 54, lymphocytes 44, and eosinophils 2. Indirect Coombs' test was negative on July 4. Cold agglutinins on July 5 were negative in 2 hours at 10° C. Bone marrow was considered "nondiagnostic" on July 7. On July 8, sickle cell determinations were negative and no L.E. cells were seen on either July 8 or August 2.

On Aug. 9, 1955, exploratory laparotomy revealed no neoplasm. Inferior vena cava ligation with bilateral ovarian vein ligation and bilateral lumbar sympathectomy were performed. Hypotension, 24 hours postoperatively, was very difficult to control despite plasma, blood (500 c.c. on August 10 and 11), and vasopressors until cortisone was employed intramuscularly, probably because of usual stress reaction and prolonged 60-day preoperative Meticorten medication which was discontinued on the day of operation. No unusual bleeding occurred during the operation. On the second postoperative day, the patient developed typical phlegmasia cerulea dolens on the right, superimposed on the bilateral phlegmasia alba dolens, which responded to extreme elevation and continuous active exercise permissible because of the inferior vena cava ligation. Superficial necrosis of toes and foot healed completely. The patient was ambulated with elastic support and discharged on the twenty-third postoperative day.

The results of complete blood counts taken on August 10 and 11 are shown in Table I. On August 10 there was anisocytosis, macrocytosis predominating, some polychromatophilia, and decreased platelets. The Lee-White coagulation time was 4 minutes, 56 seconds, and bleeding time was 2 minutes, 3 seconds. Platelets were 120,000, sodium 142.5 mEq./L., potassium 5.3 mEq./L., and chlorides 93.3 mEq./L. On August 11, results of blood smears were essentially unchanged. Creatinine was 1.9 mg. per cent, and glucose 155 mg. per cent. Blood smear results were unchanged on August 12 and nonprotein nitrogen was 38.7 mg. per cent. Fibrinolysis was negative on both August 10 and 12. On August 22 cells were unchanged but toxic granulations were observed. Complete blood counts taken on August 12, 13, 15, and 22 are shown in Table I.

TABLE I. RESULTS OF COMPLETE BLOOD COUNTS

DATE	HB (%)	RBC (MILLION)	C.I.	WBC	SEGS.	STABS	LYMPHOCYTES	MONOCYTES	EOSINOPHILS	NORMOBLASTS	UNCLASSIFIED
Aug. 10	52.5 (7.66 Gm.)	1.90	1.3	2,150	35	—	58	5	1	1	1
Aug. 11	56.0 (8.70 Gm.)	2.24	1.2	2,000	50	—	43	5	2	—	—
Aug. 12	59.0 (8.60 Gm.)	2.50	1.1	2,000	57	4	33	4	—	—	2
Aug. 13	64.0 (9.41 Gm.)	3.01	—	4,150	62	—	38	—	—	—	—
Aug. 15	Results essentially the same										
Aug. 22	56.0 (8.15 Gm.)	2.62	1.0	6,200	33	10	30	7	—	2	20

On August 24 reticulocytes were 2.8 per cent. Van den Bergh test results were total 0.5, direct 0.1, and indirect 0.4 mg. per cent. Results of indirect Coombs' test were negative. Bone marrow tests were repeated on August 25 because of abnormal peripheral blood findings and unexplained progressive anemia. The report stated: "The bone marrow consists of suspension of cells. No megakaryocytes seen. The majority of cells are blasts and promyelocytes, many of which have a monocytic appearance. The erythroid series is considerably diminished and of normoblastic development. Impression: acute myelo-monocytic leukemia."

Hemogram on August 29, 2 days after a third 500 c.c. blood transfusion, showed hemoglobin 57.5 per cent (8.38 Gm.), red blood cells 2.67 million, color index 1.0, white blood cells 1,150, stabs 4, segmented cells 17, lymphocytes 39, monocytes 22, blasts 9, and unclassified 9.

Urinalysis was always and repeatedly essentially negative.

The patient was readmitted from Oct. 13 to 16, 1955, on an emergency basis for severe headache and vomiting, dizziness, vertigo, and complete loss of vision associated with

papilledema, retinal hemorrhages, and exudate of 4 weeks' duration. She had been on Aminopterin therapy and 4 blood transfusions had been given the previous week. Radiation therapy to the head in small doses was contemplated but considered of no avail.

The woman died at home on Oct. 18, 1955, of leukemia with diffuse generalized leukemic meningeal involvement, right facial palsy, extreme swelling of the left side of the face, and stupor.

The next case illustrates the difficulties frequently encountered in the medical treatment of migratory thrombophlebitis and points out that the underlying disease need not always be malignant in character.

CASE 4.—F. McE., a 44-year-old white housewife, developed ankle edema and painful swelling of the knees while in New York in June, 1953. She was found to have tenderness in both calves and along the medial aspect of both thighs with focal tenderness of the various long veins and palpable thrombosed superficial long saphenous veins. She was hospitalized and anticoagulant Dicumarol therapy was begun. On July 7, with prothrombin time of 25 seconds, she had a questionable pulmonary embolus. Five days later, a similar but more severe episode left no clinical doubt regarding embolism even though the prothrombin time had been 35 seconds the previous day and was 45 seconds the next day. Because of abdominal tenderness, deep abdominal thrombophlebitis was diagnosed and it was believed that "ligation of the femoral veins was not indicated."

Later she received Priscoline, 25 mg. 4 times a day, for transient arterial spasm and marked coldness of the feet, with relief. Complete diagnostic survey, except for intravenous pyelography which could not be carried out because of iodine sensitivity, showed no pathologic findings.

The woman was discharged on Aug. 18, 1953, with ambulatory Dicumarol therapy and elastic support. Prothrombin levels were maintained in the range of 35 seconds on 50 to 100 mg. Dicumarol but on Oct. 1, 1953, 50 mg. of vitamin K_1 oxide (Mephyton) was given intravenously for external hemorrhoidal rectal bleeding and was repeated the next day when the patient insisted on returning to Puerto Rico, where she arrived on Oct. 3, 1953.

In view of the recent bleeding, the initial Dicumarol doses given to re-establish anticoagulant therapy were even lower than those usually employed in Puerto Rico. Response was slow, as has been previously noted in other cases, as a result of continued use of milk of magnesia and mineral oil for rectal symptoms. Three weeks later, despite adequate 35-second prothrombin levels, the patient complained of pains in the lateral and posterior aspects of both thighs and in the gluteal regions without any local signs.

Priscoline was used satisfactorily to relieve night cramps during the third month of treatment. Pain recurred along the medial aspect of the lower two-thirds of the right thigh and the middle third of the leg with calf tenderness during low prothrombin levels of 20 seconds in mid-December. The patient also complained of exertional dyspnea and precordial pain one month later despite levels of 35 seconds.

In mid-February Dicumarol was gradually decreased, and was discontinued on March 2. Because of severe pain in the right hip and calf, the patient resumed Dicumarol therapy on her own.

During the 2 months to the end of April, the patient lost her appetite, had dysphagia, and tightness in the throat. She began to dread the weekly venipuncture and yet the fear of possible emboli was becoming a phobia. She felt and looked miserable.

Because of definite small thrombosed veins (the first ever seen by us in this patient) in the mid-third of the left arm and in the left costal margin despite prothrombin levels of 33 seconds, the patient finally consented to another complete diagnostic survey. On the day of admission, April 25, 1954, 3 additional distinct thrombosed veins appeared in the right leg and another in the left thigh. Results of all diagnostic procedures were negative, including those from retrograde pyelography. The woman was discharged on April 30 to be readmitted for exploratory operation at a later time. Because of hematuria which had persisted since instrumentation and severe pain in the right kidney region, she was

readmitted on May 2. Forty-eight hours after the last 100 mg. dose of Dicumarol on April 30, the prothrombin time had been 63 seconds. It was 64 seconds the next day and 59 seconds on May 5. Fifty milligrams of Mephyton (vitamin K_1 oxide) in 200 c.c. 5 per cent glucose in water was given intravenously on this day and 6 hours later the prothrombin time was 17 seconds.

The next day, May 6, 1954, exploratory laparotomy revealed no malignancy. The preoperative plan was carried out—inferior vena cava ligation with bilateral ovarian vein ligation, and bilateral lumbar sympathectomy, from the lower border of the third to the same border of the fifth lumbar vertebra as delineated by silver clips, for arterial deficiency substantiated by skin temperatures taken on several occasions (Fig. 1).

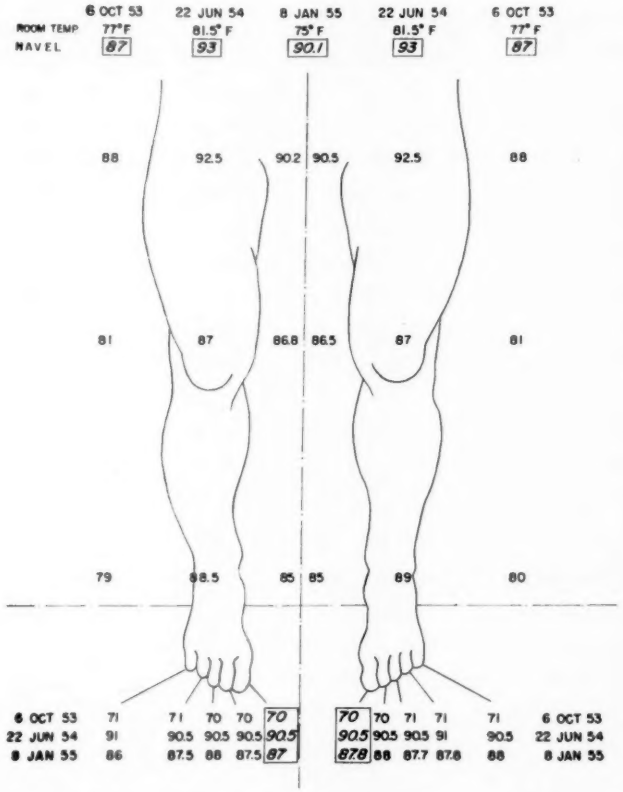

Fig. 1.—Skin temperatures, with a U.M.A. thermocouple, on Oct. 6, 1953, June 22, 1954 (47 days after operation), and Jan. 9, 1955 (8 months after operation). The temperatures in slanting numerals within squares stress the salient pre- and postoperative findings. Note the 17° F. difference between navel and great toe preoperatively as compared to the average 2.7° F. difference postoperatively.

The postoperative course was complicated by severe urinary infection with *Bacillus proteus*, dating from the cystoscopic examination, and for which no chemotherapy or antibiotics could be used because of the patient's hypersensitivity to them.

She was discharged on May 22, 1954, but was readmitted 3 weeks later with a short loop, closed, intestinal obstruction which responded readily to long-tube decompression.

Since the last discharge on June 19, 1954, the woman had been asymptomatic except for small thromboses in the right deltoid region, right thigh, and right leg which recurred once in December, 1954.

The patient has had 3 subsequent admissions. One was from May 30 to June 5, 1956, for (1) migratory thrombophlebitis, cause undetermined, and (2) heart disease, undiagnosed, possibly coronary occlusion, secondary to the thrombophlebitis with positive transient

electrocardiographic findings (possibly visceral Buerger's disease). The second admission was from Feb. 15 to 17, 1957, for dilatation and curettage because of menometrorrhagia. The third was from April 23 to 27, 1957, for excision, per anal route, of a 4 by 3 cm. rectal villous adenoma diagnosed by sigmoidoscopy with otherwise negative radiographic colon studies. In December, 1959, the patient was still free of malignant disease and asymptomatic.

DISCUSSION

The futility of superficial femoral vein ligations for the prevention of embolization, even if the phlebitic process should appear to be confined clinically at below knee level, has not been stressed sufficiently in the literature. McLachlin and Paterson[8] have shown through anatomic dissections that in 10 per cent the venous pathway from the leg is via the profunda femoris and that 37 out of 76 thrombi dissected in 100 autopsies were above the usual site of superficial femoral vein ligation so that such a procedure would not have altered the outcome in 21 of 34 cases. Venographic studies have demonstrated direct communications between the profunda femoris and the superficial femoral veins.[7] Evidence against this ligation can also be inferred from the report by O'Keefe[9] on the lack of demonstrable change in venous circulation after prophylactic superficial femoral vein ligation—if blood bypasses the obstruction through large channels, so could clots. If operation is contemplated to prevent fatal embolization, the only procedure indicated is inferior vena cava ligation.

Milk of magnesia and mineral oil seem to interfere with the absorption of oral anticoagulants. Conversely, oral antibiotics kill or greatly disturb intestinal bacterial flora, the production of vitamin K is sharply diminished, and the action of anticoagulant drugs is unrestrained.[11]

Arterial insufficiency of some degree is frequently observed associated with peripheral thrombophlebitis in patients who do not have clinically proved thromboangiitis or arteriosclerosis obliterans, Raynaud's syndrome, or collagen diseases. That this finding is of significance in the mechanism of intravascular thrombosis we do not know, but we wonder whether this diminished arterial flow may not provide a factor of stasis or sluggishness and thus cause predisposition to the phlebitis. Once this process is initiated as a trigger factor in the leg, the physicochemical reaction[6] may perhaps extend to other regions of the body. This would explain why occasionally the phlebitis occurs elsewhere.

SUMMARY

Two cases of malignant neoplasm are presented briefly, and one of leukemia and one of arterial insufficiency are reported in detail.

Exploratory laparotomy despite negative diagnostic surveys should not be delayed in patients over 40 who develop migratory thrombophlebitis which does not respond satisfactorily to anticoagulants.

Inferior vena cava ligation is the surgical treatment of choice for those in whom no neoplasm is found as it is for those in whom anticoagulants cannot be used for any reason (individual sensitivity or lack of adequate laboratory facilities).

Sequelae of inferior vena cava ligation such as those described by Shea and Robertson[10] need not be dreaded if proper elastic support and other medical measures are employed.[1, 2]

Lumbar sympathectomy should be performed if arterial insufficiency is evident in order to promote increased arterial blood flow and remove one of the possible factors responsible for peripheral thromboses.

Migratory thrombophlebitis still remains a most challenging therapeutic problem.

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RADIOACTIVE GOLD TECHNIQUE FOR THE ESTIMATION OF LIVER BLOOD FLOW: NORMAL VALUES AND TECHNICAL CONSIDERATIONS

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WHEN a colloidal suspension is injected intravenously, its particles are promptly removed by the reticuloendothelial system. It has been found that the reticuloendothelium of the liver is responsible for 90 per cent or more of this removal[7, 14] and that the liver and the spleen together account for as much as 95 to 98 per cent.[15] Since the spleen drains into the portal system, its circulation is a part of the portal circulation of the liver. This phenomenon establishes a parallelism between the rate of disappearance of the colloid and liver blood flow.[13] When colloidal Au^{198} is used, the emission of gamma rays by this isotope permits measurements by external counting of the rate of its disappearance from the blood or uptake by the liver.

The estimation of liver blood flow with radioactive colloidal gold does not require any surgical manipulation and the measurements can be repeated many times provided small amounts are used. A further advantage over methods based on the Fick principle is that the calculations do not depend on samples taken from one hepatic vein and this prevents sampling errors.

This study was undertaken to establish the normal values and range of normal variation in liver blood flow. The reproducibility of the results and the influence of experimental conditions such as dissection of the portal vein proximal to the liver were considered important to serve as a basis for further experimental studies on liver blood flow. We have given particular attention to specific detail in the technique in order to improve the accuracy of the results and minimize the amount of radioactive gold required.

EXPERIMENTAL AND CLINICAL METHOD

Forty-three mongrel dogs weighing from 9 to 47 pounds were fasted for 4 hours and anesthetized with intravenous pentobarbital sodium. After an interval of 30 minutes, the count was begun. Counts were made twice in 2 hours in 14 dogs and the second count was made up to 1½ hours after the anesthetic. Nine of the 14 animals had undergone dissection of approximately 5 cm. of porta hepatis proximal to the liver.

A scintillation counter,* with an aluminum foil in immediate contact with the crystal and a lead protection surrounding the case, was placed in the anterolateral part of the neck behind the shoulder. This arrangement places

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*Nuclear Chicago, Model 1620A.

the crystal within a few millimeters of the skin and permits readings over a wide area. It was thus possible to use very minute amounts of gold and eliminate many of the undesirable fluctuations. In 16 dogs in which the liver uptake was measured simultaneously, another counter was placed in the region of the liver.

Approximately 5 μc of colloidal radiogold* was injected intravenously in the hind leg which was then elevated for a few seconds and the needle removed without application of pressure to the vein. We kept a careful check always to be sure that no part of the animal's body was under pressure that might produce venous congestion. This may happen very easily if the counter on the neck is compressing the venous drainage of the head. Such types of technical errors produce unexpected elevation and irregularities in the graphs.

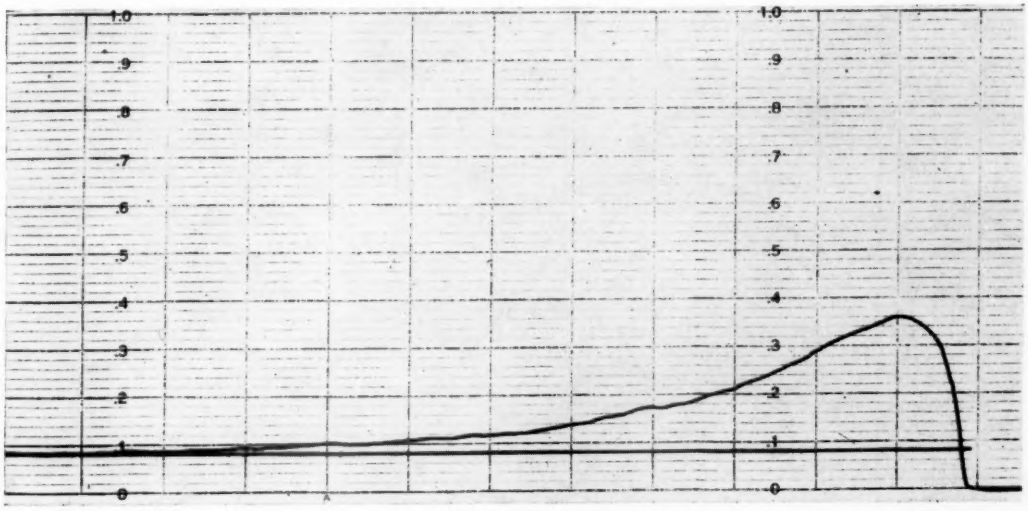

Fig. 1.—Record of disappearance obtained by external counting (dog No. 42). The heavy line at the bottom shows the level of residual radioactivity. The record was run 4 minutes longer, as shown in the picture.

In addition, the liver blood flow was measured in 11 patients with no evidence of liver disease. The technique used was the same except that the counter was placed over the head in the temporal area, and the amount of radioactive gold was increased to 10 μc.

Records† were run until no appreciable disappearance or uptake could be detected (usually about 15 to 20 minutes), and this level was used as a base line for plotting the curve on semilogarithmic paper (Figs. 1 and 2). The use of this new base line permitted calculation of the disappearance rate of the particles capable of being removed. The uptake records were run in similar fashion until a maximum level was attained. For the construction of the graphs, the activity at minute intervals was subtracted from the maximum value. Further analysis of the curves was not considered of practical value. Instead, the rate of the first 4 minutes was used to calculate the half-life (T ½). The fraction of the

*Aureotope (Squibb radiogold). Eighty-five to 100 per cent of the particles range from 3 to 10μ according to the Squibb Institute for Medical Research.

†Rectilinear Recorder, Texas Instrument, Inc.

total blood volume perfusing the liver in 1 minute, $k^{min.-1}$, is calculated by the formula, $k^{min.-1} = \frac{0.693}{T\ 1/2}$.

To avoid the introduction of additional error, the liver flow is reported as $k^{min.-1}$. For the sake of permitting easy comparison with previous reports, we have given some of our data also in milliliters per kilogram per minute. In this case, we estimated the total blood volume on a uniform basis of 95 ml. per kilogram of body weight.

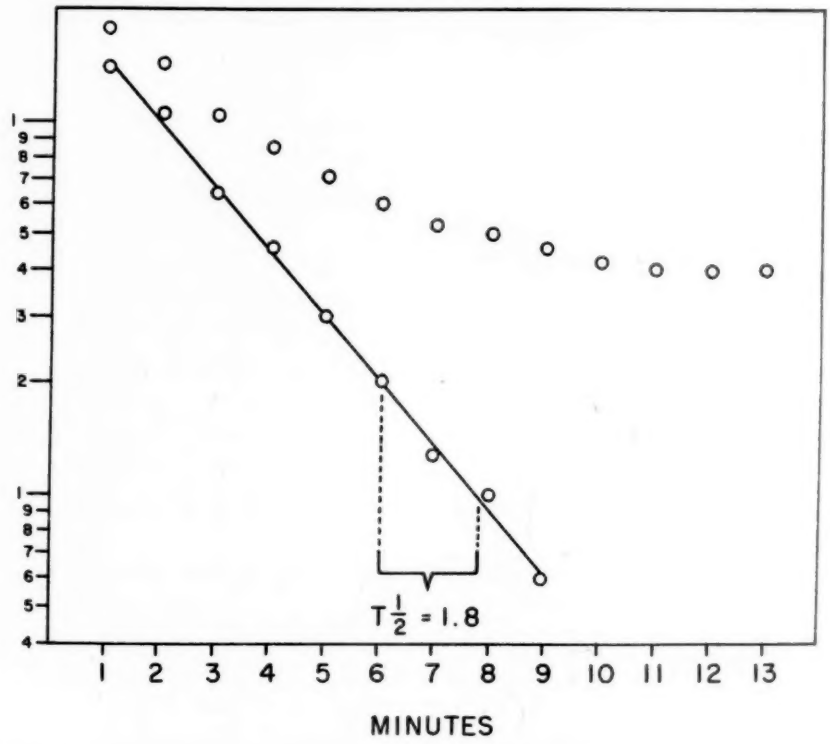

Fig. 2.—Disappearance curve shown in same animal as in Fig. 1 (dog No. 42). A true exponential disappearance is obtained after analysis for residual radioactivity.

In order to have an idea of the efficiency with which the dog liver removed the colloid we were using, we injected a known amount of radioactive gold into the portal vein and one-half hour later we injected the same amount in a peripheral vein. In both cases the peripheral activity was recorded until no disappearance was noticed. Comparison of the 2 curves permitted a simple calculation of the over-all efficiency and the efficiency for particles capable of being removed.

RESULTS

Table I shows the results obtained in a heterogeneous group of 43 dogs with an average weight of 24.2 pounds. The values of $k^{min.-1}$ (disappearance) ranged from 0.315 to 0.693, and averaged 0.483 ± 0.086. The data were divided into 3 groups according to weight of the dogs. An inverse relation between mean

values of $k^{min.-1}$ and body weight was found (Fig. 3). The number of dogs, means, and standard deviations of the groups are shown in Table II. The difference between the means of the first and third groups is highly significant (less than 0.00005 per cent due to chance).

Fig. 4 shows the results in the group of 14 dogs counted twice within 2 hours. It can be seen that the results were reproduced within 12 per cent in 13 of the 14 dogs, or 93 per cent. Data concerning 9 dogs in which a subcostal

TABLE I. ESTIMATED HEPATIC BLOOD FLOW IN 43 DOGS

DOG NO.	WEIGHT (LB.)	$T_{1/2}$		$K^{min.-1}$	
		UPTAKE	DISAPPEARANCE	UPTAKE	DISAPPEARANCE
1	16	0.93	1.16	0.745	0.597
2	16	—	1.2	—	0.578
3	18	—	1.1	—	0.630
4	15	—	1.3	—	0.533
5	12	—	1.4	—	0.495
6	11	—	1.3	—	0.533
7	9	—	1.2	—	0.578
8	18	—	1.5	—	0.462
9	16	1.15	1.25	0.602	0.554
10	15	0.9	1.2	0.554	0.578
11	17	—	1.2	—	0.578
12	15	—	1.0	—	0.693
13	28	1.2	1.45	0.578	0.495
14	20	1.2	1.95	0.578	0.355
15	27	1.2	1.3	0.578	0.533
16	25	2.15	2.0	0.322	0.347
17	23	—	1.3	—	0.533
18	29	—	1.2	—	0.578
19	20	—	1.5	—	0.462
20	21	—	1.5	—	0.462
21	25	—	1.4	—	0.495
22	20	—	1.7	—	0.408
23	23	—	2.0	—	0.347
24	23	—	1.0	—	0.693
25	27	1.3	1.35	0.533	0.513
26	28	1.25	1.5	0.554	0.462
27	26	1.65	1.55	0.420	0.447
28	22	1.27	1.4	0.554	0.495
29	26	1.3	1.5	0.533	0.462
30	25	1.3	1.5	0.533	0.462
31	29	2.8	2.2	0.247	0.315
32	25	—	1.7	—	0.408
33	24	—	1.45	—	0.495
34	21	—	1.7	—	0.408
35	36	1.5	1.9	0.462	0.364
36	34	—	1.5	—	0.462
37	30	—	1.5	—	0.462
38	47	—	1.7	—	0.408
39	39	—	1.3	—	0.533
40	41	—	1.7	—	0.408
41	37	—	1.7	—	0.408
42	30	—	1.8	—	0.385
43	30	1.7	1.7	0.408	0.408
Total	1040	22.72	63.76	8.409	20.786
Number	43	16	43	16	43
Mean	24.2	1.42	1.48	0.525	0.483
Standard deviation	—	±0.46	±0.27	±0.103	±0.086

incision plus dissection of the portal vein proximal to the liver had been carried out previous to the second count were incorporated in the same table with those on 5 dogs without operation because there was no appreciable difference between

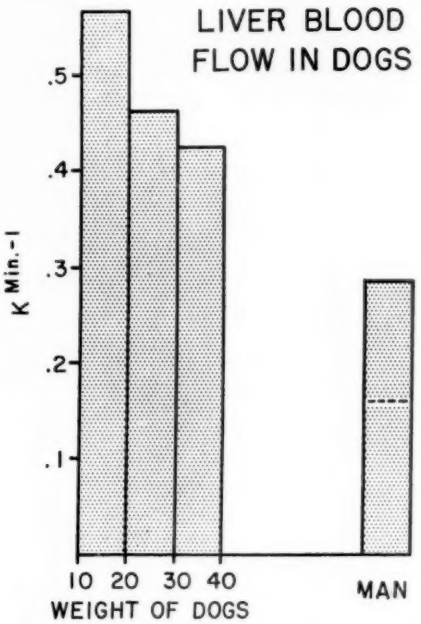

Fig. 3.—Mean values of k. Notice the inverse relation between blood flow and body weight.

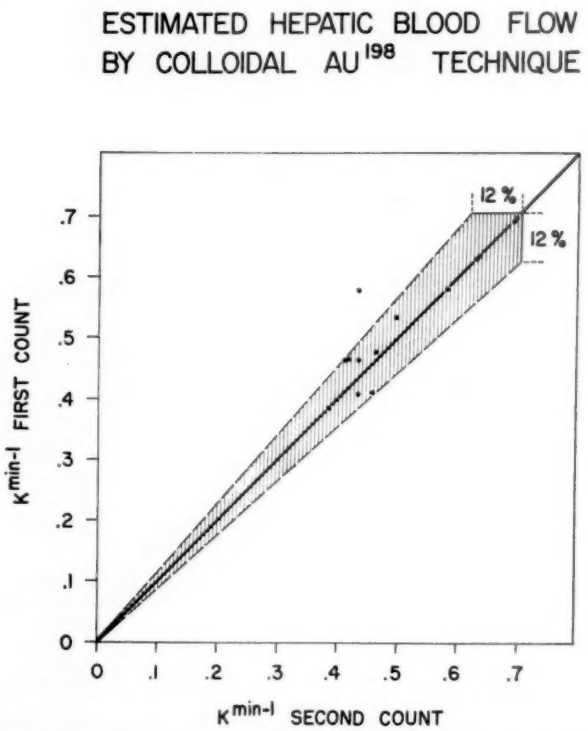

Fig. 4.—Results obtained in 2 measurements. The shaded area includes values reproduced within 12 per cent.

TABLE II. ESTIMATED HEPATIC BLOOD FLOW FOR GROUPS OF DOGS OF DIFFERENT WEIGHTS

RELATION BETWEEN LIVER BLOOD FLOW AND BODY WEIGHT IN DOG				
	WEIGHT	T ½	K	ML./KG./MIN.
0 to 19 pounds				
Total	178	14.81	6.809	
Number	12	12	12	
Mean	14.83			
	(6.74 Kg.)	1.23	.567	53.86
Standard deviation	—	±0.12	±0.049	±4.6
20 to 29 pounds				
Total	538	34.15	10.139	
Number	22	22	22	
Mean	25.45			
	(11.57 Kg.)	1.55	.461	43.79
Standard deviation	—	±0.27	±0.072	±6.8
30 pounds				
Total	324	14.80	3.838	
Number	9	9	9	
Mean	36			
	(16.36 Kg.)	1.64	.426	40.47
Standard deviation	—	±0.17	±0.048	±4.55

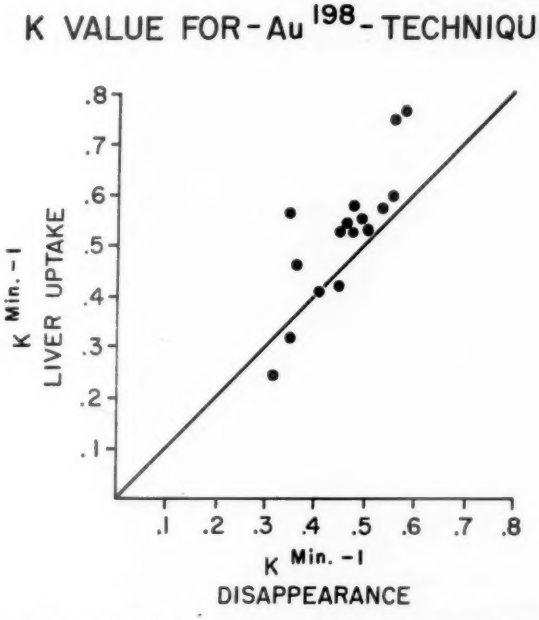

Fig. 5.—Comparison between disappearance and uptake values.

these 2 groups. The mean $K^{min.-1}$ for the first count is 0.528 and for the second count is 0.510. The difference between these 2 means is not statistically significant.

The results in 16 dogs in which disappearance and uptake were measured simultaneously are illustrated in Fig. 5. A tendency toward higher blood flow values, when these were calculated from the uptake, was noticed but there was no constant relationship. Our experience was that the reproducibility of the measurements was not as close with the counter over the liver as with the counter

on the neck. For these reasons we discontinued the liver uptake count in the remainder of the animals.

The results in 3 dogs, in which a known amount of radioactive gold was injected into the portal vein and one-half hour later the same dose injected peripherally, showed an efficiency of 80 per cent for total particles. When the residual radiation, representing particles which are not suitable for removal by the reticuloendothelium, was subtracted the effiiciency was found to be as high as 90 per cent.

In the 11 normal patients, the k values ranged from 0.433 to 0.231 and averaged 0.290 ± 0.052 (Table III).

TABLE III. ESTIMATED HEPATIC BLOOD FLOW IN 11 PATIENTS WITHOUT LIVER DISEASE

PATIENT NO.	DIAGNOSIS	SEX AND AGE	T ½	K
1	Gastric ulcer	M 46	2.5	0.277
2	Auricular septal defect	M 46	2.2	0.315
3	Cerebral vascular accident	M 69	2.6	0.266
4	Nontoxic goiter	F 39	1.6	0.433
5	Chronic mastitis	F 49	3.0	0.231
6	Inguinal hernia	M 55	2.6	0.266
7	Gastric ulcer	M 52	2.2	0.315
8	Recurrent hernia	M 46	2.6	0.266
9	Stasis ulcer (leg)	M 59	2.6	0.266
10	Peptic ulcer	M 66	2.2	0.266
11	Gangrene of hand	M 47	2.8	0.248
Mean				0.290
Standard deviation				±0.052

DISCUSSION

With these studies we have attempted to standardize and evaluate a simple and reliable technique and to establish normal values.

When the residual radioactivity level was used as a base line, it was observed that, in most cases, the rate of disappearance was uniformly constant and in only a few instances was there a change to a slower slope. In these cases the fastest or initial slope was the one used for the calculations. From these observations, we assume that in most cases the colloidal particles are, for practical purposes, either removed at a constant rate or are never removed.

In order to better evaluate our data, we thought it important to have an idea of the efficiency with which the dog liver removed the colloid. With this purpose in mind, we injected a known amount of colloid into the portal vein and compared it with the records obtained with the same amount injected in a peripheral vein. In both cases the peripheral activity was recorded until no disappearance was noticeable. The over-all efficiency and the efficiency for particles capable of being removed could thus be determined. The over-all efficiency was about 80 per cent, which is in agreement with the data reported in the literature for Au^{198} [16] and other colloids,[1] and the efficiency for particles suitable for removal was found to be close to 90 per cent. Because the particles which are never removed are excluded in the calculations, we concluded that the values reported here can be considered as 90 per cent of the actual liver blood flow. It must be pointed out that this test assumes the nonexistence of portal

systemic collaterals and, for this reason, the results must be interpreted as minimum efficiency. Vetter,[16] in a comparative study of the Bromsulphalein and radiogold methods, pointed out that his results with radiogold averaged 84 per cent of those with BSP. This slight discrepancy can easily be explained since the BSP method overestimates the liver blood flow. [2, 11, 12]

In a summary of the literature presented by Fisher,[6] it is interesting to note the wide range of liver blood flow values reported by different groups utilizing the BSP method (from 27.6 to 56 ml. per kilogram per minute). Fisher's mean value in a series of 20 dogs with a mean weight of 11.8 kilograms (49 ± 7.4 ml. per kilogram per minute) is very close to ours for dogs of 11.47 kilograms mean weight (44 ± 7 ml. per kilogram per minute). Our mean values are higher than those reported by Burkle and Giedman[3] (35 ± 5.8) with the radiogold technique.

Our mean k for normal man compares favorably with those reported by Dobson and colleagues,[5] Vetter and associates,[15] Biozzi and his group,[1] and Nardi and Palazzi,[9] but is higher than those reported by Krook,[8] Riddel and associates,[10] and Burkle and Giedman[3] (Table IV). Their values are similar to those obtained in this study before analysis of the curves for residual radioactivity.

It was surprising to find no significant difference between 9 dogs in which a major surgical procedure (laparotomy and dissection of 5 cm. length of the portal vein proximal to the liver) had been performed between counts, and 5 dogs which underwent no operation. In both groups the results were reproduced within 12 per cent (except for one dog not operated upon). A slight tendency to lower values in the second count, which may have been the result of prolonged anesthesia, was noticed in both groups.

The liver blood flow in normal dogs fluctuated widely in our group of 43 dogs weighing from 9 to 47 pounds, yet the values ranged closer to the mean when they were distributed in groups of more uniform weight. A consistent inverse relation between mean values of k and weight was found and we believe this might help to clarify the dissimilarity of the figures reported in the literature.

SUMMARY

A simple technique for the estimation of hepatic blood flow with colloidal Au^{198} is presented and evaluated. As little as 5 μc for dogs and 10 μc for man is needed and it is mandatory that interference with peripheral venous drainage be avoided during the test. The calculations must be based on the disappearance rate of the particles suitable for being removed and, for this reason, it is important that the records give information on the residual radioactivity. The efficiency of the liver was found to be about 90 per cent for the removal of those particles suitable for being phagocytized. The values obtained may then be interpreted as 90 per cent of the actual liver blood flow.

The hepatic blood flow was estimated in 43 dogs and in 11 patients without liver disease from the disappearance rate of colloidal radiogold. A statistically significant inverse relation between liver blood flow and weight has been found. The mean liver blood flow for dogs weighing less than 20 pounds was 53.8 ±

4.6 ml. per kilogram per minute. For dogs between 20 and 29 pounds it was 43.8 ± 6.8 ml. per kilogram per minute, and for dogs of more than 30 pounds, 40.5 ± 4.55 ml. per kilogram per minute.

The mean k for man was found to be 0.290 ± 0.052, which is in close agreement with several previous reports (Table IV).

TABLE IV. MEAN ESTIMATED NORMAL HEPATIC BLOOD FLOW IN MAN
COLLOID DISAPPEARANCE BLOOD FLOW VALUES

INVESTIGATOR	TECHNIQUE	MEAN	STANDARD DEVIATION
Biozzi	Complex denatured albumin	0.260	±0.062
Burkle	Au^{198}	0.196	±0.055
Dobson	Chromic phosphate	0.282	±0.008
Krook	Au^{198}	0.158	±0.021
Nardi	Chromic phosphate	0.335	±0.040
Riddel	Au^{198}	0.141	—
Vetter	Au^{198}	0.269	±0.012
Restrepo	Au^{198}	0.290	±0.052

The liver blood flow values were reproduced within 12 per cent in 13 or 14 dogs counted twice in 2 hours. No significant change in blood flow could be detected in 9 dogs in which the portal vein had been dissected between counts. More reliable results were obtained when the liver blood flow calculations were based on the rate of disappearance rather than on the uptake rate of the liver.

We wish to express our appreciation to Norman R. Dahm and Charles W. Cummings who served as student fellows on this study.

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THE EFFECT OF ACUTE HEMORRHAGE UPON HEPATIC BLOOD FLOW AND SPLANCHNIC OXYGEN CONSUMPTION IN DOGS

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A METHOD was previously described for sampling the constituents of hepatic venous blood in dogs.[2] A common hepatic vein was utilized as the sampling site. This vein is created by exclusion of the inferior vena cava above the liver from the inferior vena cava below the liver. Thus, blood samples drawn from the common hepatic vein are undiluted by blood from venous drainage areas caudad to the liver. Furthermore, these samples are representative of blood from all lobes of the liver. By means of the indicator dilution technique, with indocyanine dye as the indicator, the average rate of hepatic blood flow was found to be 56 ml. per kilogram of body weight per minute.[2] The purpose of this report is to present data on hepatic blood flow and oxygen consumption of the liver and the viscera drained by the portal vein.

MATERIALS AND METHODS

Adult mongrel dogs weighing between 13 and 22 kilograms were used for these experiments. The animals used earlier in these experiments were prepared according to the method previously described.[2] Briefly, this method consisted of inserting one end of a siliconized plastic tube into the distal end of the divided inferior vena cava caudad to the liver. The other end of this tube was inserted into the azygos vein near its junction with the superior vena cava. The phrenic veins were ligated. The majority of dogs, however, were prepared by removal of the left kidney to reduce blood flow in the inferior vena cava. This vessel was ligated and divided just distal to the liver.[12] Blood from the distal inferior vena cava was transported to the superior vena cava via venous collaterals which rapidly dilated in the anterior abdominal wall and retroperitoneal space. In both groups of animals, siliconized polyethylene catheters were passed through the external jugular vein to the inferior vena cava just proximal to the liver. These catheters were carefully positioned to lie at a constant location caudad to the heart and just cephalad to the hepatic veins. Blood specimens obtained from a catheter in this location are representative of blood from all lobes of the liver but contain no blood from extrahepatic sources. In all dogs, a second siliconized polyethylene catheter was inserted into a mesenteric vein and advanced to a constant location in the portal vein. The catheters were filled with heparin-saline solution and their distal ends heat sealed and buried in the subcutaneous tissues. They have remained patent as long as 3 months.

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All animals were allowed to recover for at least 2 weeks. The subsequent hepatic blood flow studies were carried out upon these prepared dogs with the use of pentobarbital sodium anesthesia and a mechanical ventilator. A siliconized polyethylene catheter was inserted into the femoral artery so that arterial blood pressure could be recorded. The distal ends of the previously placed catheters were dissected from the subcutaneous tissues and the sealed tips cut. Two milligrams of heparin per kilogram of body weight was injected intravenously. Hepatic blood flow was measured by use of the indicator dilution technique. Indocyanine (Cardio-green) was employed as the indicator because of its independence of variations in the spectral transmission of oxyhemoglobin and reduced hemoglobin.[5] Approximately 0.1 mg. of the dye in a calibrated syringe was injected into the portal catheter as rapidly as possible and immediately flushed with 10 ml. of sterile saline solution. Hepatic venous blood was continuously drawn via the catheter in the proximal inferior vena cava through a densitometer cuvette into a sterile flask. An average of 30 ml. of blood was removed during the performance of 1 determination. This blood could be returned to the animal as required. The resultant curve of dye concentration was visually and photographically recorded on a multiple channel oscilloscope. Total hepatic blood flow was calculated with the formula of Hamilton and coworkers[8] for indicator dilution curves. Arterial, portal, and hepatic venous blood samples were obtained in 7 experiments and oxygen content measured according to the method of Van Slyke and Neil.[17] The oxygen consumption of the liver and the viscera drained by the portal vein was calculated by multiplying the difference in oxygen content of the arterial and hepatic venous samples by the hepatic blood flow.

After the initial hepatic blood flow measurements, the dogs were bled rapidly into sterile containers either to a known volume of shed blood relative to the weight of the animal or to various levels of mean arterial blood pressure. Approximately 5 minutes was required for each period of hemorrhage. Hepatic blood flow was determined again and in 7 experiments blood was removed for determination of oxygen content. In some animals, hemorrhagic shock was allowed to progress to such a degree that transfusion of blood failed to produce a significant rise in arterial blood pressure. These dogs died rapidly. In others, transfusion of blood allowed the arterial blood pressure to rise to prehemorrhagic levels and the hepatic blood flow and oxygen content determinations were repeated. Frequently, it was possible to study these animals at 3 or 4 intervals during the production of hemorrhagic shock. The blood pressure always was allowed to stabilize before a determination was made. The minimum interval between dye injections was 10 minutes, but usually the period was nearer 30 minutes. Surviving dogs were used repeatedly.

RESULTS

Sixty-two measurements of hepatic blood flow were made in 20 dogs. Typical dye dilution curves before and after hemorrhage are shown in Fig. 1. The distribution of the individual hepatic blood flow values plotted against mean

arterial blood pressure is illustrated in Fig. 2. The range of variation of hepatic blood flow measurements decreases with lower mean arterial blood pressure. Fig. 3 shows the average hepatic blood flow at mean arterial pressures from 20 to 140 mm.Hg. The average hepatic blood flow at a mean arterial blood

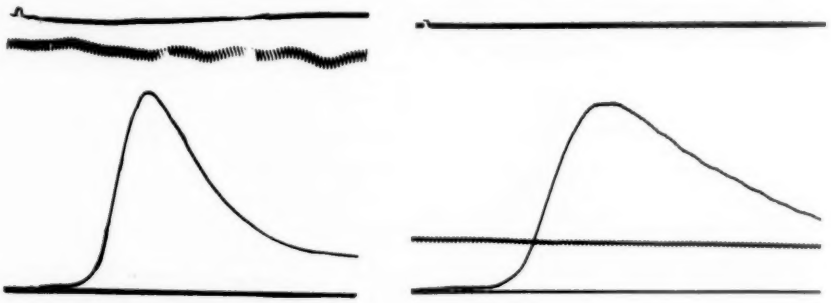

Fig. 1.—Typical blood flow tracings before and after hemorrhage. The uppermost tracing indicates the time of injection. The middle tracing represents the mean arterial blood pressure. The lower tracing is the base line from which the indicator dilution curve rises. In the experiment on the left, the arterial blood pressure was 120 mm.Hg and the hepatic blood flow 52 ml. per kilogram per minute. After hemorrhage, the blood pressure was 25 mm.Hg and the hepatic blood flow 29 ml. per kilogram per minute.

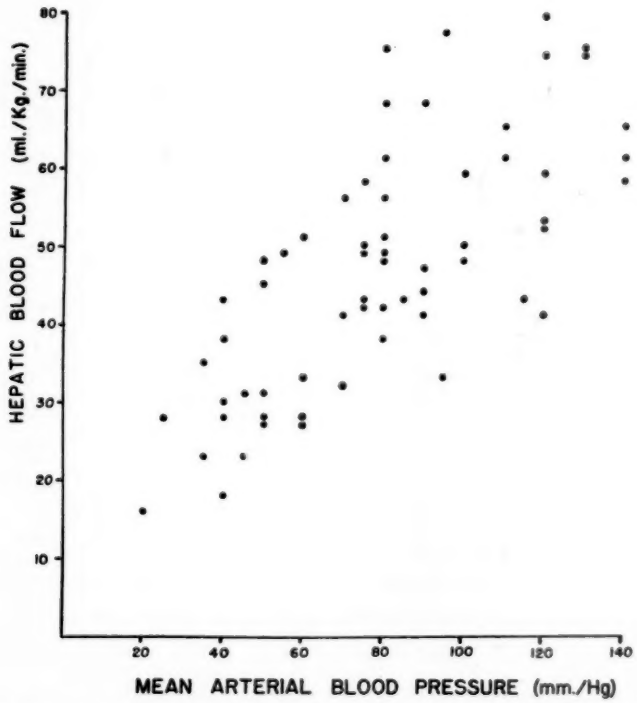

Fig. 2.—The results of 62 individual hepatic blood flow measurements plotted against mean arterial blood pressure.

pressure of 130 mm.Hg is based upon only 2 individual determinations. If these rather high values are excluded, the average rate of hepatic blood flow remains between 50 and 60 ml. per kilogram per minute when the mean arterial blood pressure is over 80 mm.Hg. Below this level, the hepatic blood flow decreases in a linear relation with the fall in blood pressure.

Blood loss was calculated as percentage of body weight in 6 animals. Hepatic blood flow in these experiments is plotted against blood loss in Fig. 4. The blood loss in these dogs averaged 2.7 per cent of the total body weight and hepatic blood flow was reduced an average of 49 per cent of control values. Again, the linear relation between the fall in hepatic blood flow and decreasing blood volume is observed.

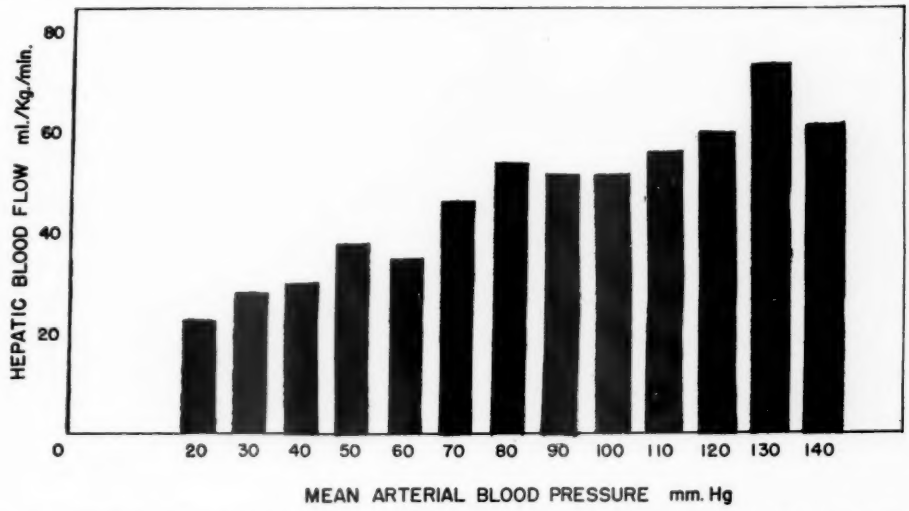

Fig. 3.—Average hepatic blood flows at mean arterial blood pressures from 20 to 140 mm.Hg.

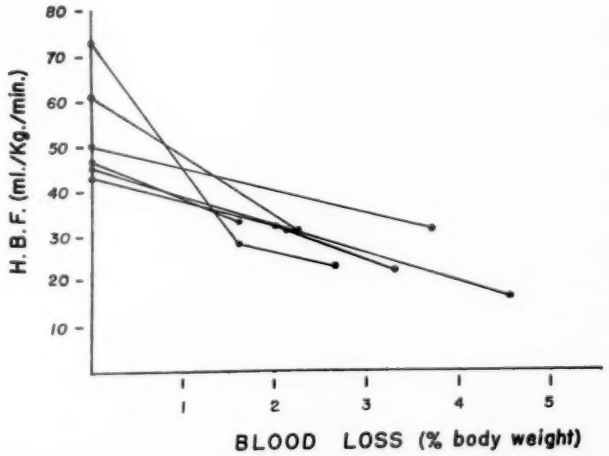

Fig. 4.—The effect of blood loss calculated as percentage of body weight upon hepatic blood flow.

The oxygen content of arterial blood before hemorrhage in 7 dogs averaged 15.9 vol. per cent, falling to 12.8 after bleeding. That of portal venous blood fell from 12.6 to 5.9 vol. per cent. The oxygen content of blood withdrawn from the common hepatic vein decreased from 11.2 to 3.6 vol. per cent after hemorrhage. The average differences in oxygen content between the sampling sites were calculated before and after hemorrhage. The artery-hepatic vein difference rose from 4.7 to 9.2, the artery-portal vein difference rose from 3.3 to 6.9, and

the portal-hepatic vein difference from 1.4 to 2.3 vol. per cent. These average values are illustrated in Fig. 5, *A* and *B*. The average oxygen consumption of the liver and the viscera drained by the portal vein was also calculated in these 7 experiments and was 2.6 ml. oxygen per kilogram per minute before hemorrhage and remained the same afterward (Fig. 6).

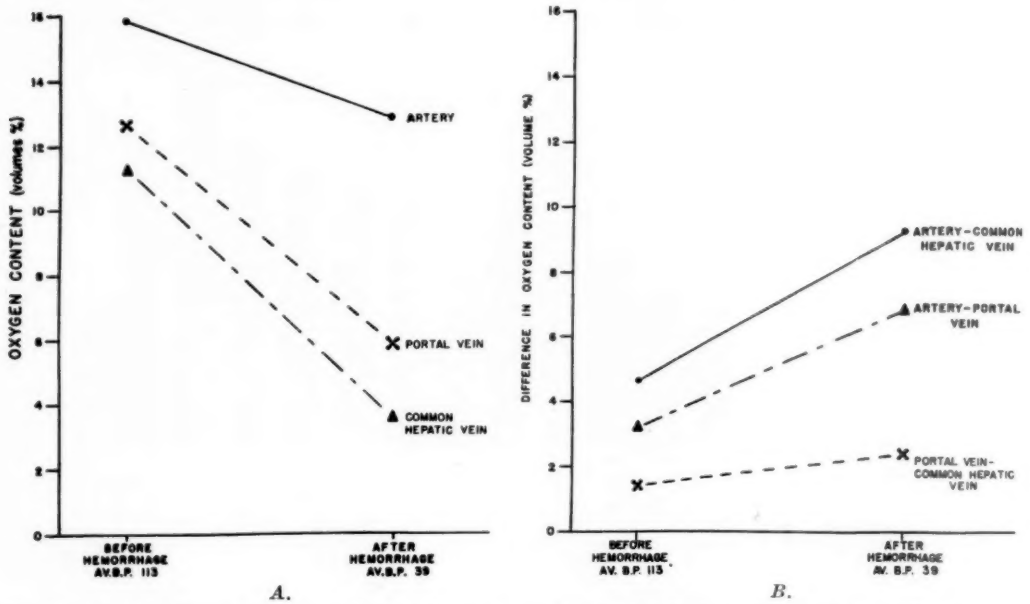

Fig. 5.—*A*, Average oxygen content before and after hemorrhage. *B*, Average difference in oxygen content before and after hemorrhage.

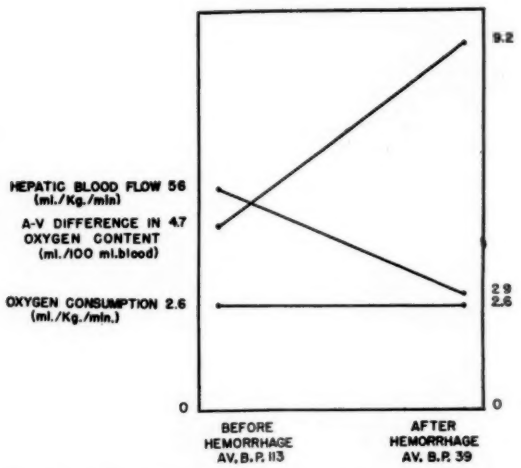

Fig. 6.—After hemorrhage, the hepatic blood flow decreases, the difference in oxygen content rises. The oxygen consumption of the liver and viscera drained by the portal vein remains unchanged.

DISCUSSION

The advantages of the method described for the measurement of hepatic blood flow and the sampling of the constituents of hepatic venous blood have been previously described from this laboratory.[1, 2] Sapirstein and Reininger[12]

and Brauer and co-workers[4] have indicated a significant error in the measurement of hepatic blood flow caused by the catheterization of a single hepatic vein. In addition, the work of Smith and others[15] has revealed that there is a marked difference in oxygen saturation in hepatic venous blood drawn simultaneously from different lobes of the liver in dogs. These experiences have convinced us that the use of a common hepatic vein previously prepared from the inferior vena cava between the liver and heart is of advantage in obtaining quantitative data regarding hepatic blood flow and the components of hepatic venous blood. Splenectomy was not carried out in these animals since both Hallett and co-workers[7] and Gilmore[6] have indicated little, if any, change in hepatic blood flow as a result of this procedure.

The independence of indocyanine of variations in the spectral transmission of oxyhemoglobin and reduced hemoglobin has been mentioned. A further advantage is its ability to mix rapidly with the blood. Wheeler[18] has shown that indocyanine is almost completely removed from the circulation by the liver. However, the time required for sufficient dye to pass through the liver to the sampling and recording system used in these experiments is never more than 30 seconds, even with the animal in profound shock. The data supplied by Wheeler indicate that only an insignificant portion of the injected dye is removed under these conditions. Thus, the hepatic blood flows that we are reporting would be only slightly higher if this error due to dye removal exists.

All reported methods show a considerable variation in the hepatic blood flow. This is caused not only by inadequacies of the method of measurement but also by real variations in flow which occur from moment to moment.[3, 16] These variations in hepatic blood flow are most marked in this study at the more normotensive levels of mean arterial blood pressure, between 80 and 140 mm.Hg, and may be due to the closing or opening of various portions of the hepatic vascular tree as noted by Knisely.[11] Fig. 3 demonstrates the more rapid decline in hepatic blood flow as the mean arterial pressure drops below 80 mm.Hg. The fall in hepatic blood flow is plotted against the blood loss expressed in percentage of total body weight in Fig. 4. These results demonstrate a linear relation between hepatic blood flow and mean arterial blood pressure and a similar relation between hepatic blood flow and blood loss. These relationships appear obvious but previous authors have attempted to place predominance on either pressure[10] or blood volume[9] decrease.

The fall in oxygen content and rise in arteriovenous and venovenous oxygen differences noted in Fig. 5, *A* and *B* have been reported by others.[6, 10, 14] Selkurt and Brecher[13] measured hepatic blood flow with a bristle flowmeter and reported a decreased oxygen utilization by the intestines and liver during prolonged shock. Apparently, in their paper, the terms oxygen utilization and oxygen consumption are used synonymously. Prolonged shock meant hemorrhage to a mean arterial pressure of about 40 mm.Hg, maintained for about 45 minutes. Under similar experimental conditions, our data indicate that the oxygen consumption of the viscera drained by the hepatic veins does not change in spite of the marked fall in hepatic blood flow. This is because of the comparable rise

in the arterial-hepatic venous oxygen gradient so that the product of these 2 values remains constant.

SUMMARY

1. Data regarding hepatic blood flow during hemorrhagic shock are presented.

2. The oxygen content of arterial, portal venous, and hepatic venous blood was determined during the course of these experiments. The oxygen difference across the mesenteric and hepatic vascular beds was calculated.

3. A linear correlation exists between hepatic blood flow and mean arterial blood pressure below 80 mm.Hg and between hepatic blood flow and blood loss.

4. During hemorrhagic shock, the oxygen content of arterial, portal venous, and hepatic venous blood falls. At the same time, the oxygen difference between these sites rises.

5. After hemorrhage to a mean arterial blood pressure of 40 mm.Hg, the oxygen consumption of the liver and the viscera drained by the portal vein is unchanged. This is because of the rise in arteriohepatic venous difference in oxygen content in spite of a fall in hepatic blood flow.

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THE ABSORPTION OF BLOOD FROM THE PLEURAL SPACE

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IT IS well known that moderate amounts of blood can be absorbed from the chest cavity in postoperative and traumatic hemothorax. In fact, it has been observed repeatedly that a remarkable degree of clearing of the pleural space usually occurs after operation or injury.[5, 8] The dynamics of this absorptive process, especially as it pertains to blood, is of considerable surgical interest. However, quantitative information on the subject is difficult to obtain clinically. In addition, few experimental data are available regarding the transfer of intrapleural erythrocytes and whole blood across the pleural membrane.

Previous reports concerning the absorption of blood from the chest can be summarized briefly. Courtice and Morris[2] labeled the erythrocytes of homologous whole blood with P^{32}, injected 1 ml. per kilogram intrapleurally in rats, and found that 70 per cent of the injected cells reached the blood stream in 5 hours. When 6 ml. per kilogram of whole blood was injected, 48 hours were required for its complete absorption. These authors noted that the rate of removal was increased by hyperventilation and decreased by respiratory depression. The only other pertinent experimental study which we have found is that of Stewart and Burgen.[11] They injected into the pleural cavity of 2 dogs a red cell suspension in which many of the cells were reticulocytes. Reticulocyte-rich blood was obtained by treating another dog with acetylphenylhydrazine for 5 days. They determined the removal of red cells by measuring the decrease in the total erythrocytes in the pleural fluid. It was not possible to measure cell removal quantitatively because of the inaccuracies of the method. They concluded, however, that red cells were absorbed as rapidly as the pleural fluid. No attempt was made by Courtice and Morris or by Stewart and Burgen to approximate the familiar clinical situation in which a large volume of blood is present in the chest.

The mechanism and pathway of pleural absorption has been thoroughly worked out.[3, 4, 12] Colloids and particulate matter are absorbed chiefly through the mediastinal and intercostal pleura in animals. There is little or no absorption through the diaphragmatic and visceral pleura. These substances pass directly through the cells of the pleural membrane, or possibly via "pores" between the cells, to enter the lymphatics. From there, colloids reach the blood stream by way of the right and left lymphatic ducts while foreign particulate matter is filtered out by the macrophages in the lymphatics and nodes. Erythrocytes

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probably follow the same route as colloids when absorbed from the chest cavity.[12]

The following experiments on dogs were carried out in order to obtain further information on the rate and extent of absorption of intrapleural blood, particularly when a large hemothorax is present. The life span of the absorbed cells was also determined.

METHODS

Mongrel dogs 11 to 19 kilograms in body weight were used. All animals were submitted to a splenectomy prior to the experiments in order to avoid the fluctuations in blood volume which occur in dogs with an intact spleen. Intravenous pentobarbital or thiopental anesthesia was used for operative procedures. The tagged erythrocytes in all experiments were prepared by the addition of 75 to 200 μc of Cr^{51} to 40 ml. of autogenous whole blood. After gentle agitation of the blood for 1 hour at room temperature, the red cells were washed twice and resuspended in normal saline. All blood samples were counted in a well-type scintillation counter in accordance with accepted standards for the measurement of radioactivity.

Four types of experiments were performed:

Experiment 1.—In 6 animals, 20 ml. of a saline suspension of red cells tagged with Cr^{51} was injected into the pleural space through a 2 cm. intercostal incision. Residual pneumothorax was minimized by aspiration of air from the chest with a catheter if necessary.

Experiment 2.—In 8 animals, 30 per cent of the estimated blood volume (assumed normal blood volume, 75 ml. per kilogram) was transferred from the femoral vein to the thoracic cavity via a closed circuit of plastic catheters. During the transfer of the blood, 20 ml. of a saline suspension of tagged red cells was injected continuously into the circuit to insure thorough mixing of tagged cells in the hemothorax (Fig. 1). Anticoagulants were not employed except for a total of 1 to 2 mg. of heparin in 20 ml. of saline used to flush the catheters.

In Experiments 1 and 2, immediately after transfer of blood to the chest cavity, the plasma volume (PV) of each animal was determined by the dye-dilution technique, with T-1824 dye. Blood samples were taken at 10, 30, and 45 minutes and dye concentration in the plasma at "O" time was derived by extrapolation. The red cell volume (RCV) was then calculated from the plasma volume by use of the whole body hematocrit (Ho). In order to obtain the whole body hematocrit, the packed cell volume (PCV) of peripheral venous blood was corrected for trapped plasma (using the factor 0.96) and multiplied by 0.88 which is the correction factor for the whole body hematocrit in dogs.[6]

Within a few hours after the injection of blood into the chest, radioactivity appeared in rapidly increasing amounts in the peripheral blood as the tagged erythrocytes were absorbed from the pleural space. In order to determine the total radioactivity in the blood stream (and hence the total volume of erythrocytes absorbed), samples of venous blood were drawn at regular

intervals; aliquots of exactly 5 ml. were lysed with saponin and counted. Counts per milliliter of red blood cells (cts./ml. RBC) were then obtained from the count on the whole blood by use of the PCV corrected for trapped plasma. The plasma of the peripheral blood contained a small amount of radioactivity only during the first few hours after injection of radioactive cells

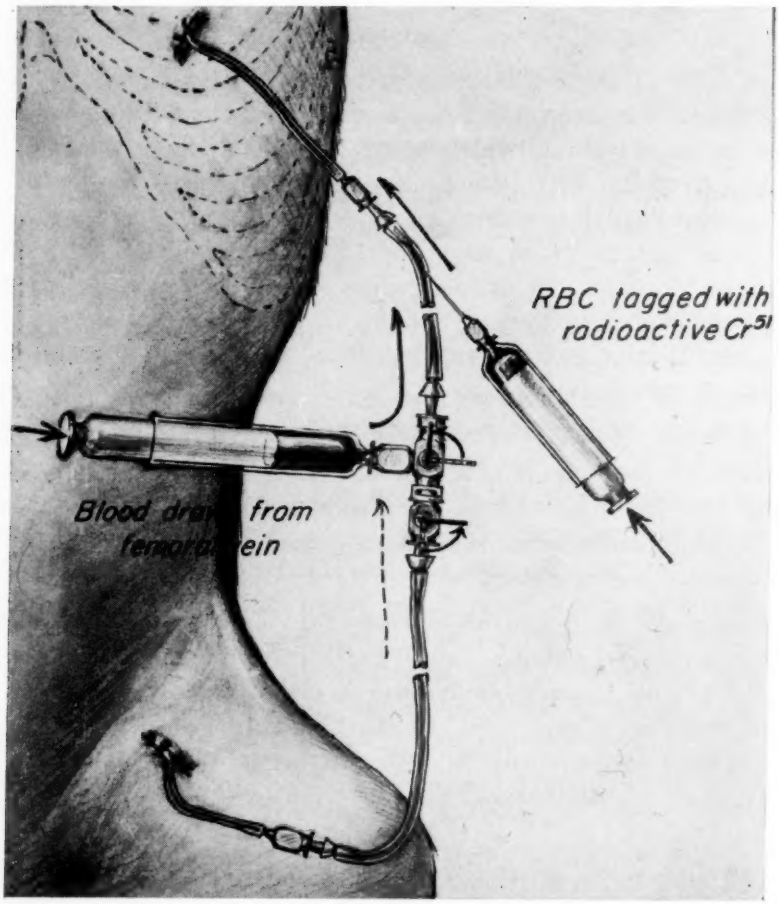

Fig. 1.—System employed in the transfer of blood from the femoral vein to the thoracic cavity in order to create a hemothorax tagged with radiochromated red cells.

into the chest. Correction was always made for plasma counts in the calculation of counts per milliliter of red blood cells. The percentage of intrapleural red cells which reached the peripheral circulation was calculated as follows:

$$PCV \times 0.96 \times 0.88 = Ho$$

$$PV \times \frac{Ho}{1 - Ho} = RCV$$

$$RCV \times \text{cts./ml. RBC} = \text{Total counts in RCV}$$

$$\frac{\text{Total counts in RCV}}{\text{Total counts on tagged cells injected into chest}} = \text{Per cent of tagged cells absorbed intact from the chest}$$

In the experiments in which 30 per cent of the animal's estimated blood volume was injected into the chest, the original RCV was corrected for the volume of cells which had returned to the circulation from the chest at the time

of the peripheral blood sample. In addition, a correction was made for the volume of red cells removed in sampling.* No correction was made for elution of Cr^{51}. All samples in a single experiment were counted together. Therefore, no correction for radioactive decay was necessary.

Experiment 3.—The apparent Cr^{51} half-life of the tagged red cells absorbed from the chest was measured in 10 animals. For comparison, the half-life of tagged red cells injected intravenously was studied in 10 animals. The initial sample for the estimation of survival in all instances was drawn 2 to 5 days after the intrathoracic or intravenous injection of the tagged cells. The counts per milliliter of red blood cells on day "O" were determined by extrapolation on semilog paper and the half-life was estimated from that point. Blood samples were taken twice weekly for 3 weeks in most instances, counts per milliliter of red blood cells were plotted on semilog paper, and the apparent Cr^{51} half-life was read from the graph. No correction was made for elution of Cr^{51} and all samples were counted together so that no correction for radioactive decay was necessary.

Experiment 4.—Tagging of erythrocytes with Cr^{51} may result in changes in the cells so that some of them are destroyed prematurely during absorption.[9] Also, inherent errors in plasma volume and in the calculated red cell volume are reflected in a wrong estimate of the percentage of erythrocytes absorbed. Therefore, the absorption of red cells from the chest was studied in this experiment by a method which avoids discrepancies from these sources. In a series of 5 dogs, 25 to 30 per cent of the whole blood volume was transferred from the femoral vein to the pleural space. At the conclusion of this transfer, the circulating red cell volume was measured by the dilution technique with erythrocytes tagged with Cr^{51}. Five days later in 4 dogs, and 6 days later in 1 dog, the red cell volume was again determined and the thoracic cavity was opened immediately thereafter. In 4 of the 5 animals the pleural space contained no blood and in the fifth animal a total of only 1.2 ml. of red cells was found. This established that the hemothorax was absorbed completely in 5 to 6 days.

In a control group of 3 dogs, the circulating red cell volume was determined immediately after 23 to 29 per cent of the whole blood volume had been removed

*The red cell volume (RCV), as determined on day "O," was corrected as follows for (1) the volume of erythrocytes absorbed from the chest and (2) the volume removed in sampling:

Symbols:

V_T = RCV, total circulating on day of sample (unknown).
V_O = RCV, total circulating on day "O" (known).
V_S = RCV, withdrawn in sampling (known).
V_I = RCV, injected into chest (known).
V_A = RCV, absorbed intact from chest (unknown).
C_A = Counts absorbed from chest (unknown). (Also total circulating counts on day of sample.)
C_S = Counts withdrawn in sampling (known).
C_I = Counts, total injected into chest (known).
C_{ml} = Counts per milliliter of circulating red cells (known).

Objective: to calculate V_T.

Equations:

$$V_T = V_O - V_S + V_A \quad (1)$$

$$C_A = (V_T \times C_{ml}) + C_S \quad (2)$$

$$V_A = \frac{C_A}{C_I} \times V_I \quad (3)$$

By substitution in (1), (2), and (3).

$$V_T = \frac{C_I (V_O - V_S) + (C_S \times V_I)}{C_I - (C_{ml} \times V_I)} \quad (4)$$

by venesection and discarded. A volume of saline equal to that of the venesection was injected into the chest cavity. Five days later the red cell volume was again measured. The purpose of these controls was to evaluate the change in the red cell volume resulting from hematopoiesis after a major hemorrhage.

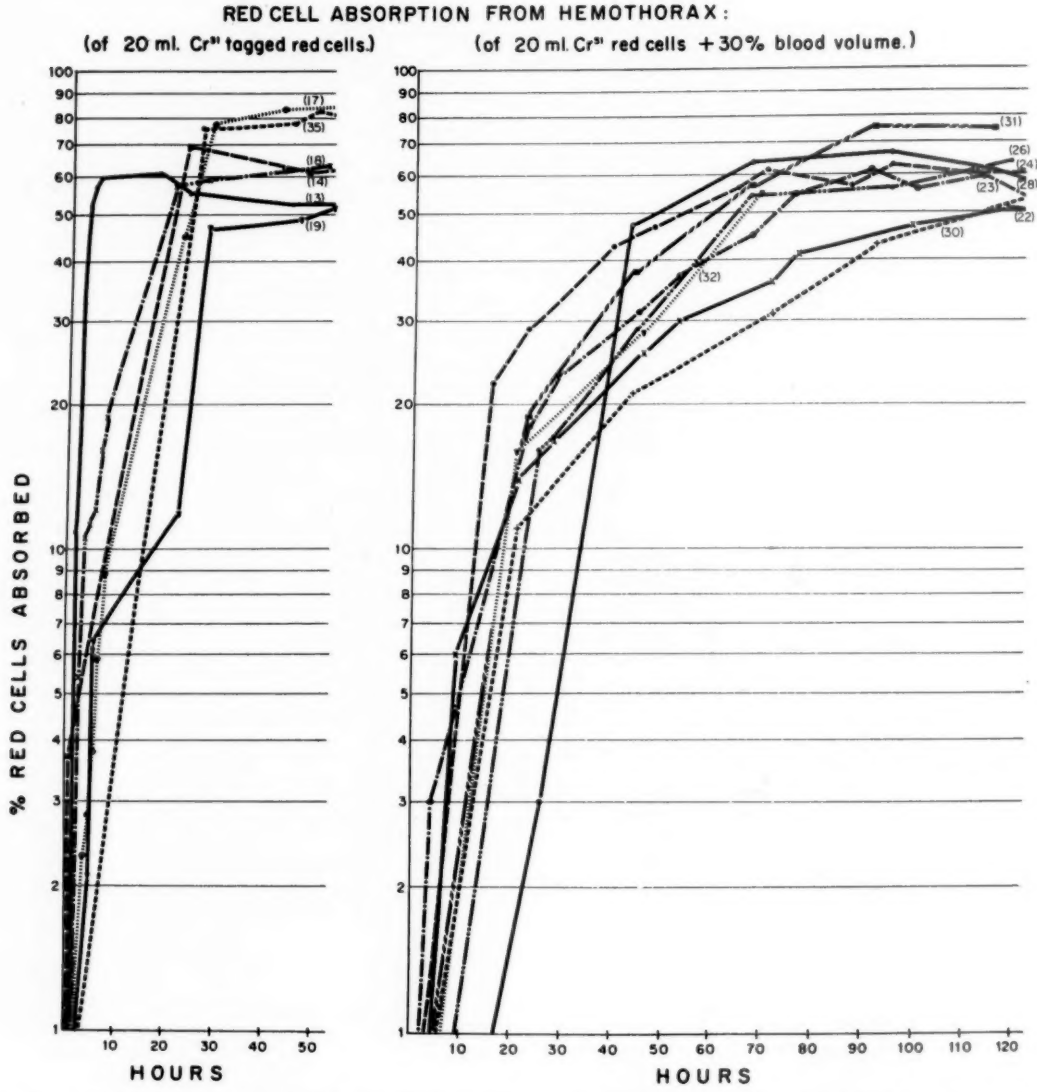

Fig. 2.—The rate of red cell absorption from the chest is plotted to demonstrate the more gradual removal of the larger volume of erythrocytes.

RESULTS

Rate of Absorption of Intrapleural Erythrocytes.—In Table I and Fig. 2 are shown the rate of absorption of red cells as determined in Experiments 1 and 2. It required approximately 30 hours for the absorption of 20 ml. of a saline suspension of tagged cells and 90 hours for the absorption of a hemothorax consisting of approximately 30 per cent of the animal's blood volume. The absorption of the large volume of whole blood was significantly slower.

TABLE I. HEMOTHORAX ABSORPTION—SUMMARY*

DOG	VOL. RED CELLS INJECTED, CHEST (ML.)	NO. HOURS FROM INJECTION→PEAK ABSORPTION	% ABSORPTION AT PEAK	REMARKS
13	5.0	6	60	Red cells tagged with Cr^{51}, suspended in saline and injected into chest (Total volume of Rbc suspension = 20 ml.)
14	5.0	24	70	
17	6.0	43	84	
18	4.0	28	59	
19	5.0	28	47	
35	6.7	50	82	
Mean ± S.E.		29.8 ± 6.29	67.0 ± 5.88	
22	161	119	51	20 ml. of suspension of tagged red cells mixed with 30% of animal's blood volume and injected into chest
23	151	92	61	
24	136	71	62	
26	89	68	54	
28	121	68	64	
30	112	141	55	
31	131	93	76	
32	120	70	65	
Mean ± S.E.		90.3 ± 18.3	61.0 ± 2.79	

*The mean time required for the absorption of 30 per cent of the animals blood volume (90 hours) was significantly longer than that required for the absorption of a 20 ml. red cell suspension (30 hours). $P = < 0.001$. The per cent absorption (67 per cent) of 20 ml. of a red cell suspension did not differ significantly from the per cent absorption (61 per cent) of a large hemothorax. $P = 0.3 - 0.4$.

Thoracotomies on several animals confirmed that absorption of the hemothorax was complete when the radioactivity in the peripheral blood reached its peak.

Extent of Absorption.—When 20 ml. of a saline suspension of tagged cells was injected into the chest, about 68 per cent of the cells appeared in the peripheral blood. When approximately 30 per cent of the animal's blood volume was mixed with tagged cells and injected into the pleural space, about 61 per cent of the tagged cells reached the circulation (Table I). However, when the absorption of intrapleural blood was determined by measuring the change in red cell volume, it seemed that all of the red cells were absorbed intact within 5 to 6 days. Actually the red cell volume increased slightly more during this period than could be accounted for by total absorption of the hemothorax. It is probable that this was the result of erythropoiesis because a similar increase in red cell volume was also noted in the venesected animals (Fig. 3).

Survival of Absorbed Cells.—The apparent Cr^{51} half-life of the tagged cells absorbed from the pleural space did not differ significantly from that of tagged cells injected intravenously (Table II). However, there were several aspects of this experiment which have a bearing on its interpretation. First, the half-life values in this series of animals were considerably lower than the reported normal range of 25 ± 2.7 days.[1] This was possibly related to the fact that each animal had undergone several previous operations with associated blood loss. An increased rate of hematopoiesis as a result of repeated hemorrhage would be reflected in a decrease in the apparent Cr^{51} half-life. Second, the same animal was used for both types of survival study in 5 instances, in each of which the erythrocyte half-life after intrapleural injection was slightly less than after intravenous injection. However, the difference was not statistically significant. The only conclusion which can be drawn from these limited

TABLE II. RED CELL SURVIVAL STUDIES*

APPARENT Cr^{51} HALF-LIFE ($T\frac{1}{2}$)					
TAGGED RBC INJECTED I.V.			TAGGED RBC ABSORBED FROM CHEST		
DOG	AV. PCV	$T\frac{1}{2}$ DAYS	DOG	AV. PCV	$T\frac{1}{2}$ DAYS
14	44	19.0	14	41	13.5
19	40	23.0	19	36	16.0
20	42	21.0	20	38	20.0
21	36	16.0	21	39	17.5
23	42	21.0	23	40	12.5
13	38	14.0	17	37	15.5
15	30	7.5	18	41	20.0
25	45	21.0	22	41	17.0
32	39	15.0	24	39	18.5
34	46	26.0	35	37	16.5
Mean $T\frac{1}{2}$ ± S.E. = 18.4 ± 1.69			Mean $T\frac{1}{2}$ ± S.E. = 16.7 ± 0.79		
S.E. of difference between means = 1.85; P = 0.3 - 0.4					

*The apparent Cr^{51} half-life of cells absorbed from the chest did not differ significantly from that of cells injected intravenously.

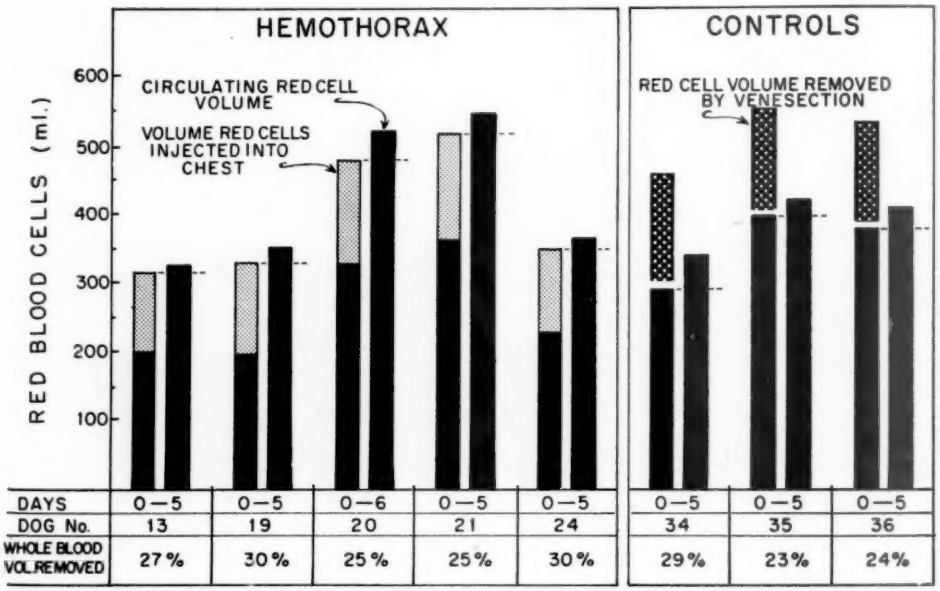

Fig. 3.—The change in circulating red cell volume over a 5- to 6-day period after the establishment of a hemothorax is shown. The circulating red cell volume was increased during this period by an amount equivalent to the red cell volume of the hemothorax, plus an additional small increment attributed to hematopoiesis. The control animals, from which blood was removed and discarded, showed only a small increase in circulating red cell volume.

observations is that tagged erythrocytes, after absorption from the chest, appear to have approximately the same survival time as tagged cells injected intravenously.

DISCUSSION

These experiments showed that erythrocytes were absorbed freely from the normal pleural space in dogs. The marked absorptive capacity of the pleura was demonstrated by the complete clearing within 5 to 6 days of a hemothorax consisting of 30 per cent of the animal's blood volume. Blood was absorbed from the chest at about the same rate as that observed from the

peritoneum. It has long been recognized that blood is absorbed rapidly after injection into the abdominal cavity. For this reason, intraperitoneal transfusions often have been administered to infants. The salient features of peritoneal absorption of blood were reviewed by Rochlin and associates,[10] who determined experimentally that, when erythrocytes tagged with Cr^{51} were injected intraperitoneally in dogs, about 70 per cent appeared in the peripheral blood in 48 to 96 hours. The survival time of the absorbed cells was normal. These findings are comparable to those we obtained on hemothorax. This is not surprising when it is considered that a broad expanse of semipermeable serous membrane overlying a network of lymphatics is available as an absorbing surface in both regions.

The proportion of intrapleural red cells which escaped hemolysis during absorption and reached the circulation intact was determined by 2 different methods—and with conflicting results. When erythrocytes tagged with Cr^{51} were used to follow the movement of blood from the pleural space, only 60 to 70 per cent of these cells could be accounted for in the peripheral blood. However, when total absorption was estimated by measuring the change in red cell volume, approximately 100 per cent of the erythrocytes returned from the hemothorax to the blood stream. It is postulated that the disparity of the results obtained by the 2 methods was primarily due to the fact that the manipulations of tagging made a portion of the tagged cells more vulnerable to destruction during absorption. Some of these altered cells were then probably eliminated by hemolysis or phagocytosis before they reached the blood stream. In addition, a small increment of tagged cells lost radioactivity through elution and, therefore, was not accounted for in the final volume of absorbed cells. Thus, the observed percentage of total absorption was lower than actual when tagged cells were placed in the chest as a tracer. It is probable that there is little loss of normal red cells during their egress from the normal pleural space.

A few comments are in order regarding the practical implications of these experiments. By inference, they support the clinical observation that the human pleura is capable of absorbing considerable quantities of blood in a few days or weeks. Under appropriate circumstances, a hemothorax is in effect returned gradually to the circulation as an autotransfusion.

The suggestion has been made that the injection of 25 to 50 ml. of blood into the pleural space in spontaneous pneumothorax will stimulate adhesions between parietal and visceral pleura.[7] Our experience would indicate that this small volume of blood is absorbed rapidly with minimal reaction and has no therapeutic value. When thoracotomy was performed 5 days after a large hemothorax in dogs, there were no adhesions, fibrin, or remarkable gross abnormality in the thoracic cavity except that the pleural surface appeared slightly edematous.

Increased respiratory activity has been shown to enhance the absorption of intrapleural blood.[2] It has also been observed experimentally that a short period of hyperventilation is followed by a prolonged effect on the absorption of fluid from the chest.[11] Thus it is to be expected that breathing exercises,

mobilization of the patient, and other forms of thoracic physiotherapy serve not only to improve pulmonary function but also to augment the clearing rate of hemothorax. Additional methods for improving the absorption of blood from the chest are being sought and experiments of the type reported here provide a base line for the evaluation of new forms of therapy.

SUMMARY

The dynamics of the absorption of blood from the pleural space was studied in dogs with the following results:

1. When 20 ml. of a saline suspension of erythrocytes tagged with Cr^{51} was injected into the pleural cavity, about 68 per cent of these cells appeared in the peripheral blood in 30 hours.

2. When 30 per cent of the animal's blood volume was mixed with tagged erythrocytes and injected into the chest, about 61 per cent of the tagged cells was absorbed in 90 hours.

3. The apparent Cr^{51} half-life of erythrocytes absorbed from the chest was approximately the same as the half-life of cells injected intravenously.

4. Absorption of hemothorax was also evaluated by determination of the change in circulating red cell volume which occurred during the 5 to 6 days after 25 to 30 per cent of the whole blood volume had been injected into the chest. This method showed that approximately 100 per cent of the red cells was absorbed intact.

It was concluded that a massive hemothorax can be rapidly and completely absorbed from the normal pleural space in dogs and that the red cells are restored intact to the peripheral circulation. The clinical significance of these findings was discussed.

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A TUBE FOR INTRAPLEURAL ASPIRATION AFTER CHEST OPERATIONS IN ANIMALS

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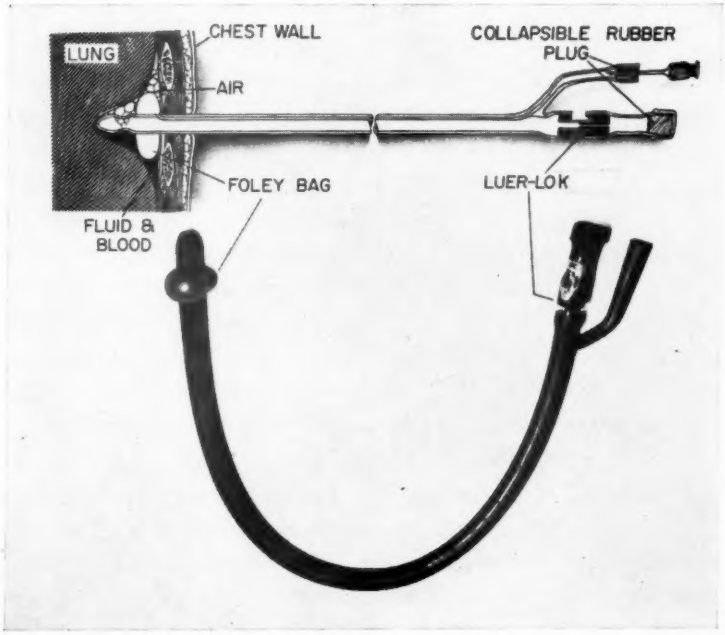
IT HAS been observed in this Laboratory on numerous occasions during a period of years that animals have died after open chest operations because of inadequate postoperative removal of intrapleural air or fluid. The prolonged continuous drainage techniques, as employed in humans after thoracotomy, are not feasible. Long tubes attached to bottles are difficult to manage; they are subject to kicking, chewing, and dislodgment by the animal.

Because we know that this problem exists in other experimental laboratories and since we have almost completely eliminated it as a source of death in open chest operations in dogs, we feel justified in describing a tube devised for this purpose (Fig. 1).



The tube consists of a No. 30 Foley catheter, the proximal end of which is sealed with a soft rubber cap, as is the side arm used for inflating the balloon. The tube is divided approximately 5 cm. from the end, and a Luer Lok attachment is inserted so that the 2 pieces of tubing may be coupled or disengaged as desired. When the tubes are separated, a Luer Lok syringe may be attached to the catheter.

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It has been our practice at the time of closure of the chest to insert the catheter through a small stab wound and to inflate the Foley bag. Positive pressure by way of an endotracheal tube is applied to permit residual air to escape from the pleural cavity. The proximal blind end is then connected to the main tubing. The tubing is covered with adhesive tape with the blind end placed at the back of the animal where it cannot be disturbed. Further aspirations, as desired, may be made by simply inserting an 18 or 19 gauge needle attached to a syringe through the rubber diaphragm at the end of the tube.

The tube is permitted to remain in the chest cavity until complete re-expansion of the lung has taken place. It is removed by simply deflating the Foley bag.

The author wishes to express his indebtedness to Dr. Bernard Fisher for his continued encouragement and direction in this study.

THE USE OF THE GREATER OMENTUM IN INTRATHORACIC SURGERY

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THE natural properties of the greater omentum are such that it plays an important part in intra-abdominal processes, covering the affected part in cases of perforation or inflammatory lesions and isolating this part from the rest of the abdominal cavity. In this way it succeeds, in most instances, in preventing the process from spreading in the peritoneum. Moreover, inflammatory changes in the omental tissue itself also remain circumscribed as a rule, as evidenced by findings obtained both during surgical intervention and at autopsy. Great use can be made of these protective properties in practice. Many authors use the omentum in abdominal operations to cover anastomoses or other sutures, as well as for sealing purposes around artificial drainage tracts. Experience shows that such measures nearly always prove dependable and are, in fact, of great value.

In the thorax, by contrast, no such organ exists. It is true that the pleural membranes exhibit similar properties, adhering rapidly and not infrequently helping to confine inflammatory processes within strict limits. However, histopathologic changes resulting from perforation or other processes in the pleural cavity often tend to spread, and the anatomic possibilities of covering and isolating such processes are very limited.

Other tissues which might be considered in this connection include the pericardial fatty tissue—the so-called thoracic omentum[4] and the lung itself.[16] Surgical covering of a defect by means of the pericardium is limited in scope. The lung, by contrast, can be displaced almost at will, and can help to cover sutures. The results have proved favorable. In the case of extensive defects of certain mediastinal organs (esophagus and trachea), when these are repaired with alloplastic material, the surgeon has no suitable tissue (such as the greater omentum in the abdominal cavity) at his disposal for covering the sutures or the plastic material. In such cases, however, the sutures between the stump of the organ and the plastic tube are bound to prove insufficient by themselves, since the mediastinal connective tissue is not able to form sufficient granulation tissue in so short a time. The consequences are nearly always fatal, and include mediastinal abscesses, pleural empyema, mediastinal emphysema, hydropneumothorax, and fistula formation. In addition, erosion of the neighboring organs by the plastic material tends to provoke severe hemorrhage and fistulas in these organs.

We have recently carried out experiments in an attempt to transpose the greater omentum into the pleural cavity through an aperture in the diaphragm.

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In so doing, we covered both the points of junction between the organ and the plastic material and the alloplastic tube itself. In a group of dogs selected for these experiments, the medial segment of the thoracic esophagus was resected and the defect bridged with a polyethylene tube. In a second group, the trachea was resected above the bifurcation and replaced by an Ivalon tube (with built-in polyethylene rings).

In order to determine the tissue reactions of both the greater omentum and the mediastinum in various phases of development, a number of the dogs were killed at different time intervals after intervention. It was found that the omentum soon gave rise to a fibrous layer which united the 2 stumps of the organ over the alloplastic tube. In this way, the tube was isolated from the rest of the mediastinum. None of the complications usually encountered after

Fig. 1.—Transverse sectional view of the medial mediastinum of a dog after plastic surgery of the esophagus. *a*, Fibrous thickening of the omental tissue round the alloplastic tube (tube removed for this picture), *b*, aorta, *c*, bronchi, *d*, fibrous granuloma. In the remaining mediastinum, apart from slight fibrinous pleurisy, no inflammatory tissue can be seen. (Courtesy of Georg Thieme Verlag: Thoraxchirurgie 4, 1957.)

such interventions were observed in this group. There were no cases of mediastinal abscess, pleural empyema, fistula formation, erosion of mediastinal organs, or bleeding from large vessels. The initial inflammatory reactions in the reticular tissue were confined to the innermost parts close to the plastic tube, and did not involve the neighboring organs. A typical fibrous tube of this kind is shown in Fig. 1. The case is that of a dog in which the medial segment of the thoracic esophagus was resected without ensuing complications. The dog was killed 8 weeks later.

Within as short a time as 24 hours, the adhesions between the end of the organ and the omentum and between the latter and the mediastinal connective tissue were so advanced that the lumen of the organ and tube were completely separate from the mediastinum and pleural cavity. By the fifth day the reticular tissue displayed marked granulation, with extensive fibroblast proliferation and an increase in macrocytes. This meant that a broad connection existed between the end of the organ (in the esophagus, the muscularis propria, and in the

trachea, the submucosa) and the reticular tissue, the collagen fibers being slightly increased. This process was more evident by the seventh day. By the fourteenth day, the reticular tissue around the plastic tube was already fibrosed,

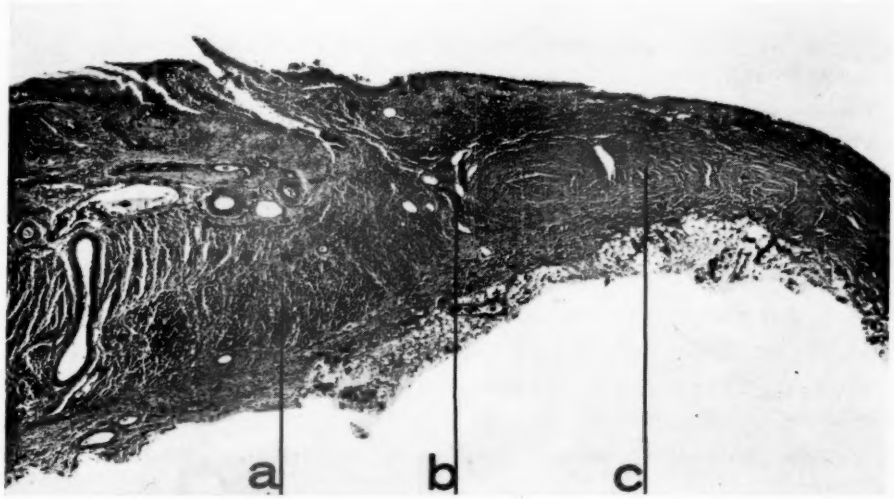

Fig. 2.—Plastic surgery of the esophagus in a dog, 14 days after intervention, with firm, fibrous connection between the stump of the esophagus and the fibrosclerotic reticular tissue. *a*, Muscularis propria of esophagus, *b*, bridge, *c*, reticular tissue. (Courtesy of Georg Thieme Verlag: Thoraxchirurgie 4, 1957.)

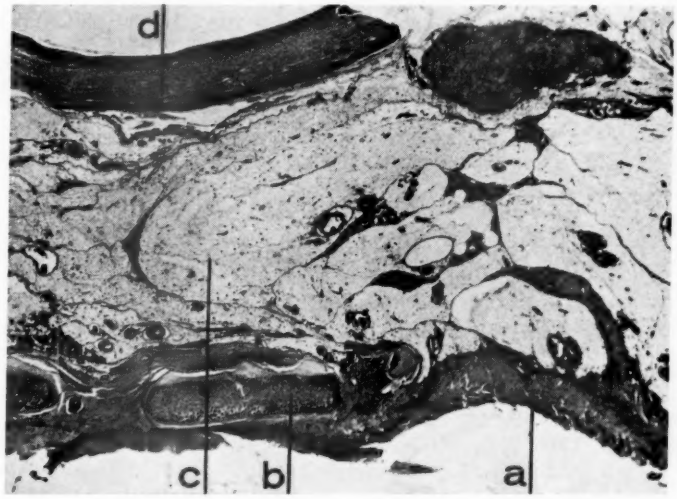

Fig. 3.—Plastic surgery of the trachea in a dog, 10 weeks after intervention. *a*, Fibrous reticular tissue surrounding the plastic tube (tube removed for this picture), *b*, stump of trachea, *c*, loose, nonsclerotic reticular tissue, *d*, aortic wall free from inflammatory lesions. The fibrous reticular tissue is firmly connected with the tracheal submucosa, the elastic layer of longitudinal fibers being split up in the process. The granulomatous changes do not involve the mediastinal organs. Note also the firm connection between the reticular tissue and the pars membranacea. (Courtesy of Georg Thieme Verlag: Thoraxchirurgie 5, 1958.)

and the initial inflammatory changes in the inner layers of the reticular tissue had almost completely subsided. The mediastinal pleura was involved in the proliferation of connective tissue, but there were no changes in the mediastinal organs themselves (Figs. 2 and 3).

At a later stage (6 months and more), the process of fibrosis became more intense, leading to contraction of the fibrous tube in craniocaudal direction. The plastic tube thus became firmly fixed. We would emphasize that the fibrosis was confined to the fibrous tube (and its inner layers in particular) and in no way involved the neighboring organs of the posterior mediastinum. The isolation of the lumen of the organ and tube was then complete, thus excluding any erosion of the neighboring organs. In spite of this, we have failed to detect any signs of epithelization of the inner wall of the fibrous tube even after periods of 12 months. As mentioned earlier, the plastic tube was fixed by the sclerotic tube of fibrous reticulum. The position of this plastic tube, moreover, depends on its length, shape, and elasticity, and more particularly on the size of the lumen, which practically determines functional sufficiency or insufficiency. In the case of the trachea, neither dislodgement or even slight displacement of the plastic tube was ever observed. In the case of the esophagus, these dangers are greater, for instance, when the tube is of too small a lumen, and so proves functionally insufficient, or when it is not of the appropriate shape. The mechanical consequences of an insufficient tube include ulcerations where the tube presses on the mucosa, dilatation of the proximal segment of the esophagus, and hyperperistalsis of the latter.

Transposition of the greater omentum without interruption of its circulation is possible in dogs and in human beings without any undue technical difficulty, even in cases where intra-abdominal interventions have been previously performed, leaving adhesions. In man, the omentum must be detached along the greater curvature, in one area from both the stomach and the transverse colon, the right gastroepiploic artery being retained on the side of the omentum. This is of vital importance, since the circulation must be maintained if the desired tissue reactions are to develop in a sufficiently short time. Otherwise, there is the danger of extensive necrosis of the omentum itself, and hence of additional intrathoracic complications. In the dog, detachment of the omentum from the stomach and transverse colon is not necessary. In none of our cases did we observe signs of strangulation at the diaphragmatic aperture or any displacement. The transposition causes no appreciable displacement of the abdominal organs, or any functional disturbances. Admittedly, an intervention such as the alloplastic replacement of part of the thoracic esophagus or trachea in man constitutes a radical operation, and may properly be rejected on various grounds. But this in no way detracts from the importance of the omentum, with its unusually favorable properties, in intrathoracic surgery. There can be no doubt that this tissue may be considered for covering intrathoracic anastomoses and other sutures, as well as fistulas and stumps, and may be used even as a palliative measure for restoring the continuity of the esophagus and the trachea, assuming, of course, that the structural conditions obtaining permit.

SUMMARY

Transposition of the greater omentum into the thoracic cavity to cover alloplastic tubes designed to replace parts of the trachea or esophagus and the points of junction of these is quickly followed by the formation of a firm, fibrous

connection between the ends of the organ. This covers the plastic material and so isolates the latter and the lumen of the organ concerned from the mediastinum. This removes all danger of the complications otherwise encountered after such interventions, such as abscess formation in the mediastinum, fistulas, pleural empyema, erosion of neighboring organs, and resultant severe hemorrhage.

It is suggested that these facts, demonstrated experimentally, may well be borne in mind in relation to intrathoracic interventions in man.

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A REGIONAL PERFUSION OXYGENATOR

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THE administration of chemotherapeutic agents of both the cytotoxic and antibacterial types has become of increased interest to the surgeon with the development of the principle of regional perfusion. As originally described by Creech and co-workers, the treatment of neoplasms limited in their extent to one anatomic area was undertaken by temporary isolation of the blood supply of that region and incorporation of the main artery and vein into an extracorporeal circuit. The tumor could then be exposed to high concentrations of cytotoxic chemicals without the danger of destruction of sensitive normal tissue in other parts of the body. A pump oxygenator was included in the extracorporeal circuit to circulate the perfusate and provide oxygenated blood.

The first to utilize this system were those surgical groups who were already equipped with oxygenators for total cardiopulmonary bypass. In most instances this equipment was expensive, cumbersome, and more complicated than was practical for regional perfusion. Early experience with such equipment provided the impetus for the search for a small disposable unit that required little preparation and provided versatility sufficient for the regional perfusion of many areas. Previous experience with the bubble oxygenator led to the selection of this oxygenating system for further trial.[1]

In cooperation with a commercial laboratory,† we have developed a simple disposable oxygenator. In addition to the oxygenator itself, a set of inlet and outlet tubes has been designed to eliminate the necessity of preparing any equipment for the extracorporeal bypass circuit.

The oxygenator bag consists of 2 large sheets of plastic which have been welded together in such a way as to form a pathway for the blood. One side of this bag has inlets at the bottom for venous blood. The blood is immediately exposed to oxygen supplied from a separate tank through a diffuser and is driven in streams of bubbles to the top of the bag. At this point the blood bubbles spill over a stainless steel sponge coated with silicone to eliminate foam. The blood progresses downward, losing any microbubbles that may remain before reaching the filter at the bottom of the bag. It then flows to the outlet set for pumping.

The inlet and outlet sets have been made to fit the oxygenator. The arterial outlet set connects directly to the filter on the oxygenator and consists of a length

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of plastic tubing, a chemotherapy inlet, pump head inserts, and further tubing to carry the blood to the patient. The inlet (venous) set has a priming inlet, pump head inserts, and sufficient tubing to connect to the bubble column. The pump inserts have been made to fit the Sigmamotor cross circulation pump or artificial kidney pump used by most groups for perfusion. The chemotherapy inlet and priming inlet will accommodate standard syringes and intravenous tubing.

When completely assembled, the oxygenator bag and inlet and outlet sets, together with the pump, make the entire extracorporeal circuit of the regional perfusion system. No metal connectors, rubber tubing, or other materials are required. The plastic unit is completely sterilized by the manufacturer.

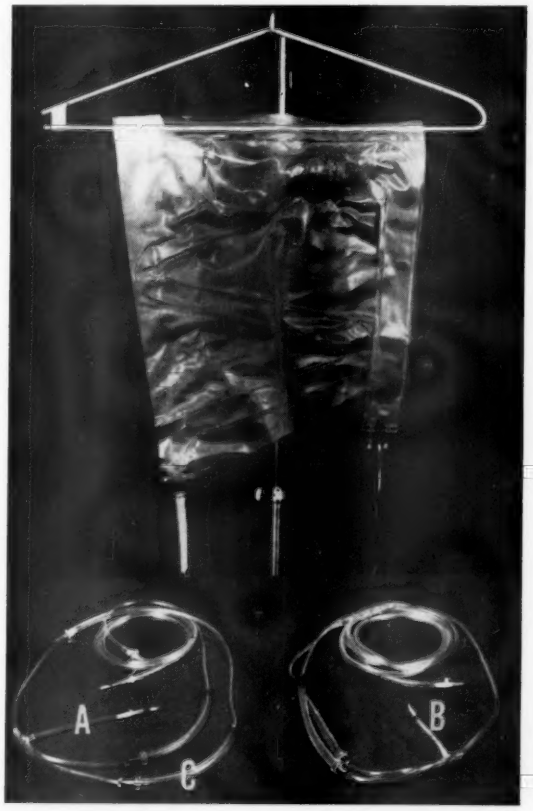

Fig. 1.—Sheet oxygenator on hanger with inlet and outlet sets. *A*, priming inlet, *B*, chemotherapy inlet, *C*, pump head for use with Sigmamotor pump.

As noted in Fig. 1, special short inlet tubes have been provided in the arterial and venous lines. Through the tube in the venous line (*A*) it is possible to prime the oxygenator without breaking the sterility of the venous set. The chemotherapy inlet (*B*) provides a place to inject the cytotoxic chemical or antibiotic and also a place to put a washing solution into the circuit to remove excess long-acting toxic chemicals from the tissue.

Laboratory trial of this unit showed it to be capable of providing 500 c.c. per minute of blood for a period of at least 1 hour without any recognizable

deterioration or wear of parts. At this level of flow the plasma hemoglobin concentration never rose above 30 mg. per cent when the pump heads (*C*) were properly adjusted. Oxygen saturation of all blood samples taken from the arterial side was above 99 per cent in experiments with 100 per cent oxygen. In other series saturation was comparable to the gas used in the oxygenator.

Clinical applications of isolated organ perfusion have been simplified with the use of this equipment. The time previously spent before actual operation in preparing the oxygenator, sterilizing connectors, and assembling parts has been eliminated. Moreover, cleanup and breakdown time is not necessary as the entire unit can be disposed of simply and quickly.

SUMMARY

1. A disposable plastic bubble oxygenator with inlet and outlet sets has been described which greatly simplifies regional perfusion. By eliminating the multitude of parts previously necessary, this system provides a safe and rapid method for supplying oxygenated blood for isolated perfusion chemotherapy.

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A CORONARY SINUS SYSTEM FOR USE DURING CARDIOPULMONARY BYPASS

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MANY of the initial problems associated with the use of pump-oxygenator systems have been solved, or have assumed less importance. One aspect of total body perfusion which has been given little attention is the "coronary sinus" return system. This aspect of perfusion is frequently overlooked as a source of increased morbidity and mortality rates, regardless of the pump-oxygenator system used. The blood involved primarily represents the coronary flow returning via the coronary sinus and Thebesian vessels emptying into the right side of the heart. This return flow has been reported to be approximately 6 to 8 per cent of the total perfusion at perfusion rates of 60 to 80 ml. per kilogram of body weight per minute.[4] In certain congenital and acquired cardiac lesions, this volume of blood will be considerable when the coronary flow is augmented by high bronchial artery or aortic regurgitant flow.†

Some surgeons have discarded all blood aspirated from the heart during bypass. Others have utilized methods which either decrease or ablate coronary return in order to minimize the problems. These methods include cardiac arrest, intermittent occlusion, and moderate to profound hypothermia.

It is obvious in certain situations, and particularly when patients have acquired valvular disease, that even when such adjunctive measures are employed the amount of blood returning to the heart can be considerable and it must be returned to the pump-oxygenator system whether desirable or not. The policy of discarding all such blood avoids the problems, but of necessity demands a blood reserve which, though large, may be inadequate.

The Problem and Purpose of This Study.—The "toxicity" of blood aspirated from the heart and returned to the main perfusion system is related to the manufacture of air bubbles at the suction tip, where an admixture of

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†The blood aspirated during open cardiotomy includes not only blood returning via the coronary sinus but also, in certain situations, blood from other sources. Consequently, the terms coronary sinus system and coronary sinus flow are misnomers. For descriptive purposes, however, these terms have been used throughout this presentation. Also, it should be pointed out that in the perusal of subsequent data, when the blood returns to the heart almost entirely via the coronary sinus, it would be incorrect to assume that the minute volume aspirated represents the actual total coronary flow.

No specific attempt was made to aspirate directly the coronary sinus ostium. The intracardiac field was cleared only sufficiently to allow surgical correction to be performed. With the heart beating, the right ventricle undoubtedly discharges the blood which it receives into the pulmonary circuit. The position of the patient on the operating table would alter the volume reaching the right ventricle.

blood and air is aspirated. If this blood is returned to the main perfusion system, fatal air embolization may occur. Whether or not this happens would appear to be dependent upon the "dose" of bubbles given to the patient. The dose, in turn, is related to the number of bubbles created per unit of blood aspirated, the volume of blood aspirated per minute, the duration of open cardiotomy, and the total volume of aspirated blood returned to the main perfusion system and thence to the patient. Aside from the minimal hemolysis of blood which occurs incidentally to the use of pumps or negative pressure, there is no other known factor which adversely affects the blood aspirated from the heart during total body bypass.

Cognizant of the problems involved, we have developed a coronary sinus system in this experimental laboratory and have used it clinically in the last 74 cases in which a pump-oxygenator was used.[3] It is the purpose of this paper to describe this unit and its behavior in the clinical situation.

DEVELOPMENTAL OBSERVATIONS

At the inception of the development of a pump-oxygenator system, designs and models of a coronary sinus bubble trap were studied in this laboratory. The use of blood plasma, as suggested by Rygg,[5] has been most helpful in the evaluation of the defoaming characteristics of any trap. Blood plasma has foaming characteristics similar to those of whole blood. Very small bubbles, unseen in whole blood, are readily visible in plasma and microbubbles can be identified with a dissecting microscope.

Bubbles of 3 to 5 mm. diameter and upward are readily broken by simple contact with certain silicones. Such bubbles also can be separated from whole blood or plasma by passage through a chamber where the velocity of the blood-gas mixture is sufficiently reduced to allow the bubbles to rise to the surface. In contrast, smaller and microscopic bubbles are exceedingly difficult to separate completely from, or to rupture in, whole blood or plasma.

Experimental studies with a number of different coronary sinus bubble traps have shown several principles that are useful in the elimination of bubbles and particulate matter. First, the method of blood aspiration from the cardiotomy should result in little air-blood mixing. Second, there should be an area where the velocity of the air-blood mixture approaches zero. Third, the bubbles should contact a defoaming agent. Fourth, an area of reduced pressure should be present to produce bubble expansion. Fifth, the blood should pass through a filter for removal of any particulate matter. These principles have been incorporated into a coronary sinus bubble trap system.

Blood Aspiration From the Cardiotomy.—Aspiration is carried out with a roller pump. The rate of the pump is regulated by a foot pedal. This pedal is at the end of an 8-foot flexible cable and is operated by the surgical assistant, with the use of the "sucker" tip to clear the surgical field. Fig. 1 is a photograph showing the foot pedal, control cable, and roller pump that constitute the aspirating system. Fig. 2 shows its position in the coronary sinus system.

When small quantities of blood flow into the operative field, the rate of the pump is low, thus reducing air-blood mixing. If the flow becomes voluminous, the rate of pumping may be rapidly accelerated, and larger volumes of blood can be easily cleared.

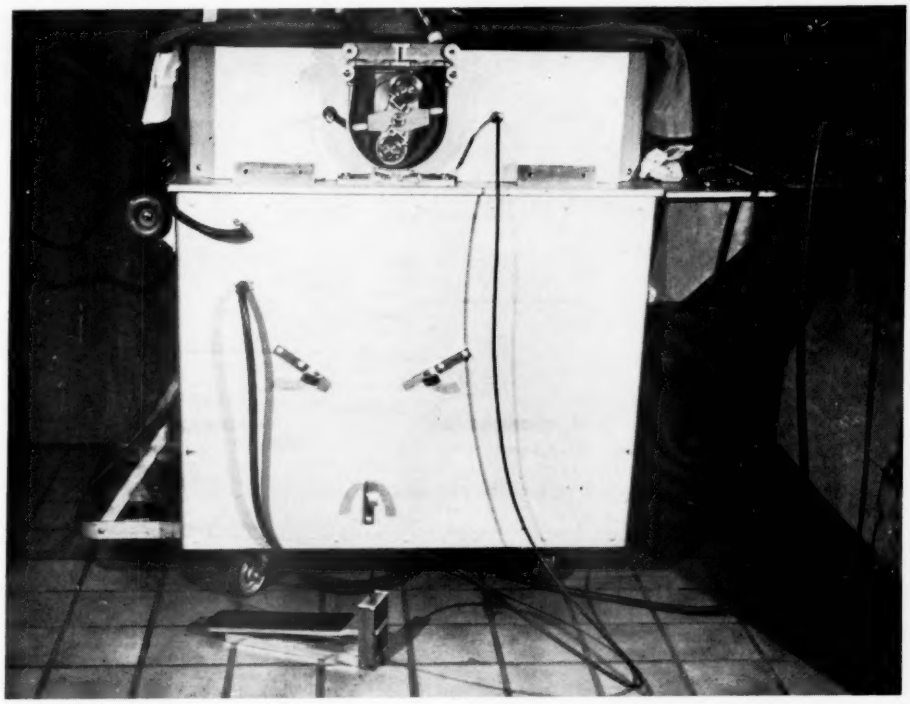

Fig. 1.—The coronary sinus pump and the foot pedal which controls it via an 8-foot flexible steel cable. This enables one member of the operating team to adjust the rate of pumping to coincide with the blood flow into the operative field. Thus the gross admixture of air with the blood is avoided.

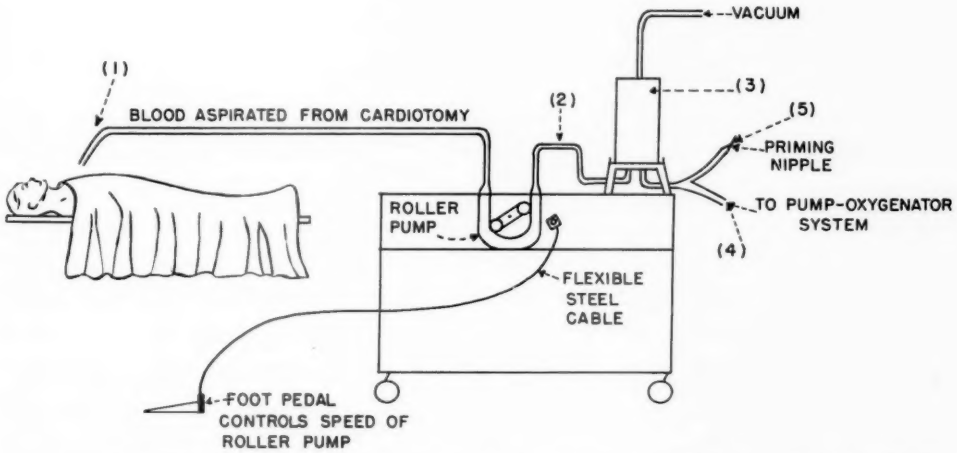

Fig. 2.—Schematic drawing of coronary sinus system. *1*, Two suction tips connected by ⅜ inch Mayon tubing and a "Y" adaptor to the negative side of a manifold in a roller pump. *2*, This manifold is connected to the input nipple of the coronary sinus bubble trap. *3*, The coronary sinus bubble trap consists of the various parts shown in Fig. 3 and diagrammed in assembled cross section in Fig. 5. *4*, The trap is connected to the pump-oxygenator system by this line. This connection is made through a "Y" adaptor into the negative or suction side of the pump-oxygenator system's venous pump. *5*, A priming nipple is connected to the "Y" adaptor in the line leading to the pump-oxygenator system.

The Area of Reduced Velocity.—Reduced velocity is incorporated in the coronary sinus system by passage of the blood through the coronary sinus bubble trap. Figs. 3, 4, and 5 show the disassembled bubble trap, the assembled trap, and a schematic cross section of the unit.

During cardiopulmonary bypass, a certain amount of blood may be lost without an immediate adverse effect on venous return or the perfusion. Thus, if the blood appearing in the surgical field is returned immediately to the coronary sinus bubble trap, it can be accumulated there for varying periods of time prior to return to the pump-oxygenator system. During this interval, the velocity of blood through the trap is zero, and there is maximum opportunity for the separation of air and blood.

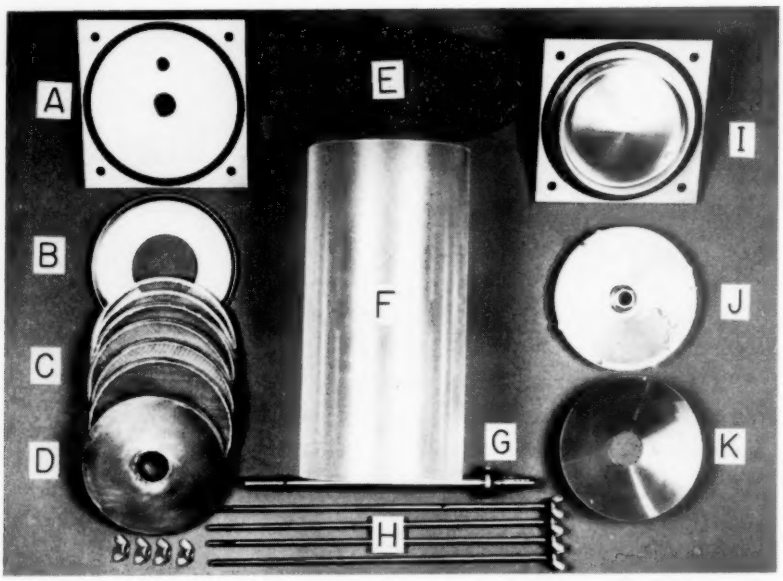

Fig. 3.—Disassembled parts of the coronary sinus bubble trap. *A*, Bottom, *B*, fixed baffle plate, *C*, six 40-mesh stainless steel screens, *D*, floating baffle plate, *E*, stainless steel sponge, *F*, outer glass cylinder, *G*, input nipple and center standpipe, *H*, rods and wing nuts for assembly, *I*, top, *J*, skimmer base plate, *K*, skimmer plate. Except for the outer glass cylinder, all the parts are made of highly polished stainless steel and are coated with Armour's Monocote. (Monocote, Formula-E, List 657, The Armour Laboratories, Armour & Co., Chicago 11, Illinois.) Recently, the floating baffle plate, fixed baffle, and skimmer base plate have been made of Teflon, because of its outstanding nonwetting properties. The outer glass cylinder is siliconized with General Electric's silicone SF-92. (Silicone SF-92, General Electric Co., Silicone Products Dept., Waterford, New York.)

The coronary sinus bubble trap is initially primed with sufficient blood to replace irretrievable losses that may occur during bypass. This blood acts as a buffer volume that maintains a low velocity through the bubble trap, even when the return from the surgical field occurs simultaneously with the transfer of blood to the pump-oxygenator system. Blood under these circumstances passes through the trap without turbulence or splashing which may carry microbubbles into the pump-oxygenator system or generate new ones (Fig. 6).

Contact With a Defoaming Agent.—As the blood enters the coronary sinus bubble trap (Fig. 5), it passes through stainless steel sponges coated with a thin layer of baked silicone antifoam compound. These sponges provide maximal opportunity for contact of the bubbles with the silicone coating.

Because this coating is very thin, the problems of antifoam embolization[2] are avoided.

Negative Pressure Area.—A negative pressure of approximately 25 mm. Hg is applied to the bubble trap chamber through the air vent (Fig. 5). Bubbles entering this negative pressure area expand. This expansion reduces the specific gravity of any bubbles immersed in the blood, and thus accelerates air-blood separation. Surface bubbles, exposed to the reduced pressure, break as they expand.

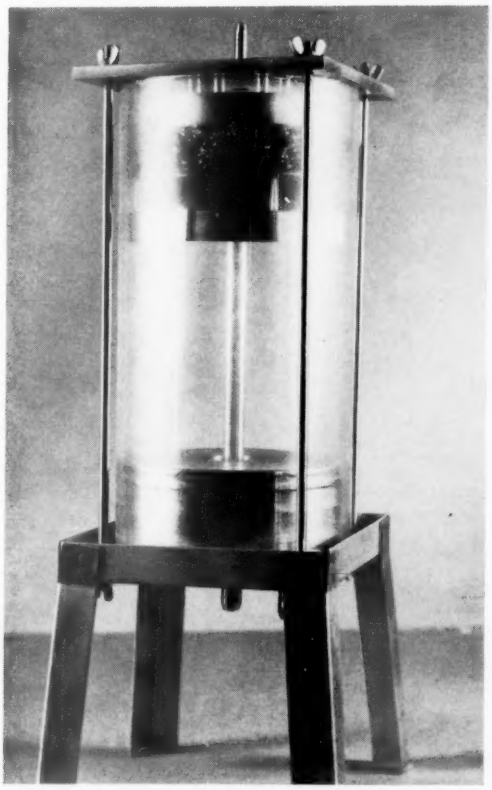

Fig. 4.—The assembled coronary sinus bubble trap. The entire unit can be assembled, wrapped, and sterilized by autoclaving. It is then ready for use at any time. Its capacity is 3,000 ml. of blood, but it may be primed initially with only 850 ml.

Filtration.—Particulate emboli, such as bits of myocardium, calcified tissue, or old thrombi, may be aspirated from the surgical field. It is essential to pass the blood through a filter to remove such particulate matter. This filtration is carried out in the bottom of the trap (Fig. 5) by passage of blood out to the pump-oxygenator system through six 40-mesh stainless steel screens.

Component Parts and Operation.—A detailed description of the various parts of the coronary sinus bubble trap, their assembly, utilization, and relationship to the pump-oxygenator system, is related in detail in the legends associated with Figs. 1 through 7. Two further points must be emphasized in relation to the operation of the coronary sinus system. First, the priming volume of the bubble trap reflects the expected irretrievable blood loss that may occur during the cardiotomy. This loss is proportionately greater in tetrads and

complicated lesions necessitating a prolonged cardiotomy, or with large flows into the operative field. The priming volume is also increased when a transsternal exposure is used, since the blood lost into the pleural cavities is not immediately retrievable. Kirklin[1] suggests that this blood lost into the pleural cavities may be immediately returned to the pump-oxygenator system by use of additional drainage lines with small pool tips inserted into these areas.

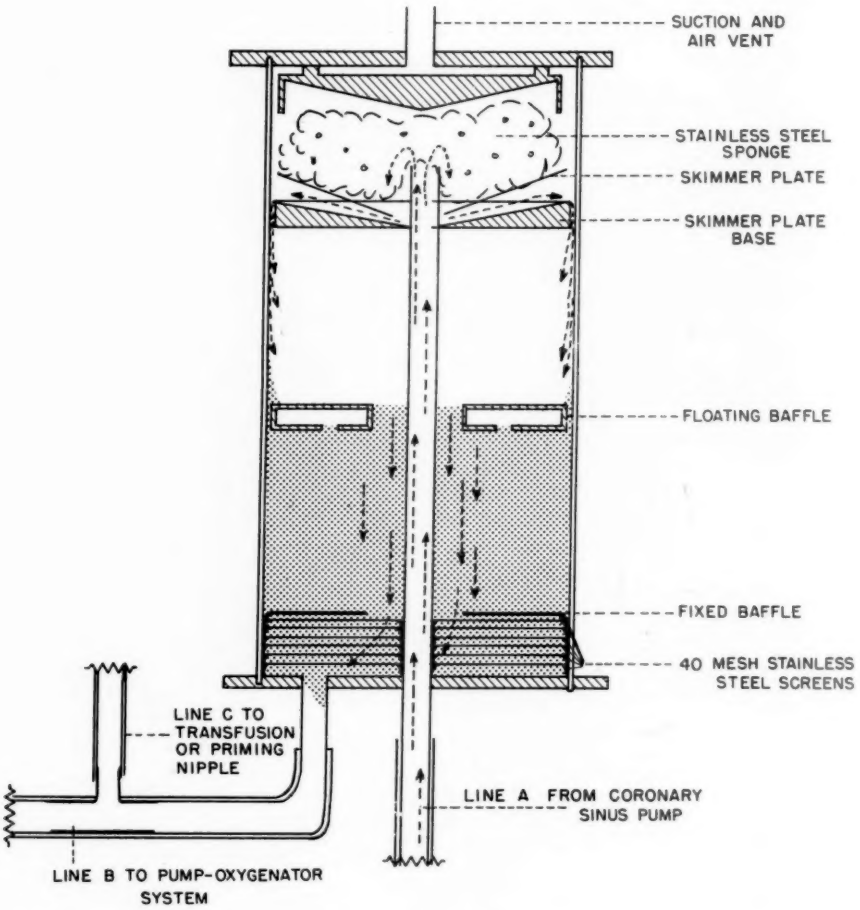

Fig. 5.—A schematic cross section showing the assembled bubble trap with arrows indicating the path of blood flow during the accumulation of the coronary sinus flow

Second, the addition of extra blood to the system during cardiopulmonary bypass should be carried out with the aid of gravity only. If the negative pressure of the bubble trap is used to draw extra blood into the system, considerable turbulence occurs in the filter chamber of the transfusion set. This generates myriads of microbubbles and draws them into the system below the screens.

CLINICAL EXPERIENCE

Presently, the coronary sinus bubble trap has been used with the pump-oxygenator system during 74 cases of open cardiotomy. Complete records are available in 35 of these instances. These data are summarized in Table I. The flow through the coronary sinus bubble trap has varied from 0 to 1,450 ml.

per minute. These flows have represented 0 to 34 per cent of the total perfusion delivered to the patient. In most instances, all of the blood pumped into the coronary sinus bubble trap has been returned to the patient. In 7 patients, none of this flow was returned, and in 3, only half of the flow was returned. Table II summarizes the average open cardiotomy time, the average flow rate, and the total flow through the coronary sinus bubble trap in several groups of patients.

In the 35 patients with adequate records, one (No. 90, Table I) failed to gain consciousness postoperatively, despite an apparently adequate perfusion. A diffuse central nervous system insult had occurred during a cardiotomy

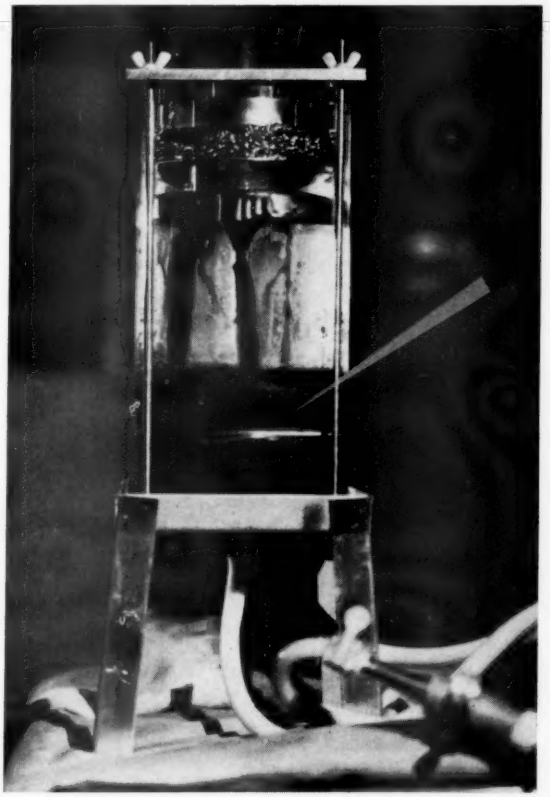

Fig. 6.—The coronary sinus bubble trap in operation, showing the even streams of blood flowing down the glass wall onto the top of the floating baffle (indicated by the arrow). Note the absence of splashing or turbulence.

requiring 64 minutes of perfusion, during which time 600 ml. of blood per minute had been passed through the coronary sinus system. While this death could conceivably have been caused by a failure of the coronary system, other patients who are all alive and well have had higher total coronary sinus flows with return of all blood into the main perfusion system.*

DISCUSSION

The coronary sinus system presented is a useful adjunct to a pump-oxygenator system. It has significantly reduced the quantities of blood needed

*A recent patient; not included in this report, made an uneventful recovery after a total flow through this coronary sinus system of approximately 60 L. of blood.

TABLE I.—SUMMARY OF PERFUSION DATA

PATIENT NO.	PERFUSION (L./M²) (ML./MIN.)		OPEN CARDIOTOMY (MIN.)	"CORONARY SINUS" FLOW			LESION*
				MILLILITERS PER MINUTE	PER CENT TOTAL PERFUSION	PER CENT OF VOLUME RETURNED TO PATIENT	
Congenital Lesions.—							
69	2.04	2,000	9	67	3.3	100	IASD
62	2.30	4,060	12	79	1.9	100	IASD
48	1.55	2,000	7	86	4.3	33	IASD
52	2.30	1,800	14	86	4.7	0	IASD, died
50	2.84	4,200	9	161	3.8	0	IASD
56	3.06	4,100	8	162	3.9	0	IASD
55	2.21	3,400	15	170	5.0	0	IASD
54	2.35	4,200	19	180	4.3	50	IASD
96	2.60	4,500	17	350	7.8	100	IASD
92	1.70	2,400	41	60	2.5	100	IASD with APVD
91	2.30	3,200	23	61	1.9	50	IASD with APVD
77	2.45	3,900	39	92.5	2.35	100	IASD with APVD and PH, died
58	2.60	4,050	30	120	2.95	100	IASD with APVD
97	2.47	5,000	41	525	10.5	100	IASD with APVD and MS
65	2.20	1,740	31	34	1.95	100	IASD with IVSD and PVS
67	1.70	600	15	0	0	0	IVSD
57	3.20	1,950	20	15	0.1	0	IVSD
76	2.45	810	31	24	2.85	100	IVSD, died
80	2.20	4,250	19	126	3.0	100	IVSD
88	2.70	3,300	27	153	4.4	100	IVSD with PH
53	1.88	1,200	32	163	14.5	100	IVSD with PH
78	3.00	2,900	30	187	6.4	100	IVSD with PH
87	2.40	3,100	56	194	6.3	100	IVSD with PH, died
82	2.35	3,150	30	327	10.4	100	IVSD with PH, died
79	2.50	2,800	34	88	3.1	100	IPS
61	2.53	3,800	11	150	4.0	100	AS
Acquired Lesions.—							
51	2.48	4,000	23	64	1.6	0	MS
49	2.67	4,000	25	393	9.8	92	MS and MI, died
83	2.00	3,800	38	452	11.1	100	MS and MI, died
90	2.30	4,200	64	600	14.3	100	MS, MI, AI, died
60	2.25	3,800	25	759	20.0	100	MS, MI, AS, AI
89	2.20	4,200	22	1,000	23.8	100	MS, MI, AI, died
95	2.65	4,250	6	1,450	34.2	100	MS, MI, AS, AI
73	2.15	3,900	35	430	11.0	100	VA, died
93	2.10	3,000	11	95	3.1	100	Rupture of SV

* IASD — interatrial septal defect.
APVD — anomalous pulmonary venous drainage.
IVSD — interventricular septal defect.
PH — pulmonary hypertension.
PVS — pulmonary valvular stenosis.
IPS — infundibular pulmonic stenosis.
MS — mitral stenosis.
AS — aortic stenosis.
MI — mitral insufficiency.
AI — aortic insufficiency.
VA — ventricular aneurysm.
SV — sinus of Valsalva.

TABLE II. THE RELATIONSHIP OF TIME AND FLOW THROUGH THE CORONARY SINUS SYSTEM WITH VARIOUS LESIONS

LESIONS	AVERAGE OPEN CARDIOTOMY TIME (MIN.)	FLOW THROUGH CORONARY SINUS SYSTEM	
		AVERAGE (ML./MIN.)	TOTAL (ML.)
Interatrial septal defect	12	150	1,800
Interatrial septal defect with anomalous pulmonary venous drainage	43	150	4,450
Interventricular septal defect	29	168	4,872
Acquired lesions of mitral valve	29	675	19,560

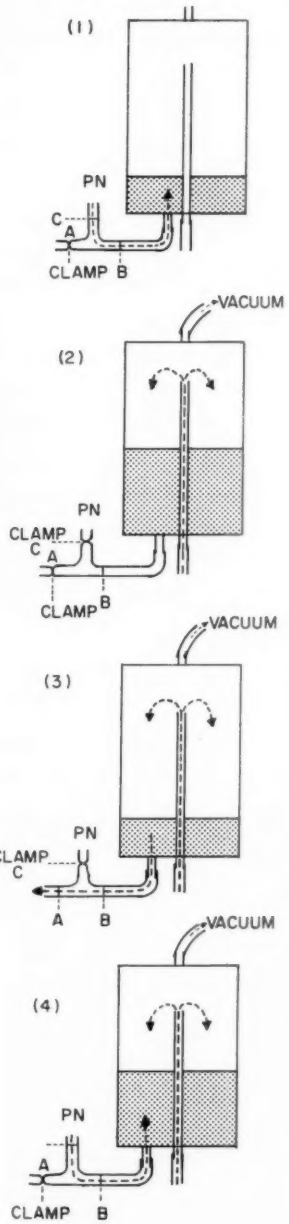

Fig. 7.—Diagrams of the flow of blood through the bubble trap during the various phases of its operation. *1, Priming.* The coronary sinus bubble trap is primed by allowing blood to flow without turbulence into the bubble trap through the priming nipple *(PN)*, while a large clamp is applied at *A*. No vacuum is created during this phase. The blood is allowed to reach a level at least above the screens and fixed baffle plate. When the trap has been primed to the desired level, a second clamp is applied at *B*. The clamp at *A* is removed and the pump-oxygenator system is primed. At the completion of this maneuver, a clamp is applied at *C* and *A* and the clamp *B* is removed. The coronary sinus bubble trap and pump-oxygenator systems are then ready for operation. *2, Accumulation of blood from the cardiotomy.* During cardiopulmonary bypass, blood flowing into the operative field is aspirated into the coronary sinus bubble trap. It is accumulated here until its volume noticeably affects the perfusion by slightly diminishing venous return, as evidenced by a fall of blood level in the oxygenator. *3, Transfer of blood to the pump-oxygenator system.* The blood accumulated in the bubble trap may be transferred to the pump-oxygenator system by release of the clamp at *A*. This allows the blood to be drawn into the pump-oxygenator system by the venous pump. When the total accumulated volume has been transferred to the perfusing system, the clamp is reapplied at *A*, and the collection of coronary sinus blood is repeated. *4, Transfusion of coronary sinus system during cardiotomy.* As the bypass continues, there is inevitably some blood lost irretrievably. These losses are first noticed when the transfer of the coronary sinus flow accumulation to the pump-oxygenator system does not entirely restore the oxygenator blood level. This level is restored by transferring extra blood to the perfusion system and thus lowering the bubble trap's priming level. The level can be restored by removal of clamp *C* while clamp *A* is kept closed. This replacement blood may then flow gently into the trap without turbulence or bubble formation. When the original priming level has been restored, the clamp is reapplied at *C*.

for intracardiac operations, because there is no hesitation in the return of large valumes of the blood aspirate back into the main perfusion system.

Patients with mitral valve lesions frequently have aortic valvular lesions which are not clinically significant, and which may even be undetectable by the cardiologist. When the patient is placed on complete cardiopulmonary bypass, the intact left side of the heart continues to contract and eject any blood regurgitating through the aortic valve. The heart appears full, and fails to assume the usual flaccid character of the empty organ on complete bypass. This failure of the bypassed heart to collapse completely should alert the surgeon to aortic regurgitation. Once the left atrium is entered, the blood is no longer ejected out into the aorta. Instead, it pours profusely and steadily into the operative field. If one is unable to retrieve this blood promptly, the entire procedure may rapidly become a surgical disaster. In such a situation, the usefulness of a large volume, efficient coronary sinus bubble trap becomes apparent.

In general, coronary sinus flow may be reduced in several ways—by chemically induced anoxia, by hypothermic cardiac arrest with cross clamping of the ascending aorta, or by intermittent occlusion of the aorta during perfusion. Such occlusion may be necessary to increase the effective total systemic perfusion and to prevent massive amounts of blood from pouring into the field through an incompetent aortic valve. The coronary sinus flow may also be reduced by use of reduced perfusion with or without hypothermia. Such maneuvers reduce the coronary flow and diminish the need for an effective coronary sinus bubble trap. The volumes of blood flowing into the operative field under these circumstances may be small. The blood can be discarded and replaced by extra transfusible blood. However, each of these procedures may represent some added risk to the patient, and is not necessarily applicable to every patient undergoing intracardiac operation.

An additional measure which appears to have merit in reducing the possibility of serious air embolization from aspirated blood has been the practice of layering the operative field with carbon dioxide. If the aspirate consists mainly of blood and carbon dioxide, the rapid diffusion of carbon dioxide should reduce markedly the opportunity for air bubbles to be manufactured.

The perfect coronary sinus bubble trap system would allow the immediate return of this blood to the pump-oxygenator. It would remove all contaminating material which would endanger the patient in any way. Through studies in the experimental laboratory, certain principles appear important in the separation of potential emboli from the coronary sinus blood flow. The bubble trap described in this paper contains features that utilize these principles to separate air and particulate material from this blood. Undoubtedly, the bubble trap only approaches the ideal. It has, however, performed well and is a very essential part of the pump-oxygenator system.

SUMMARY

During extracorporeal circulation, the volume of blood removed from the open heart varies considerably from case to case. Unfortunately, blood aspirated

from the open heart represents an admixture of blood and air. Because of the possible danger of returning this mixture to the main perfusion system, some have elected to minimize the risk by the utilization of hypothermia (thereby reducing the total perfusion and coronary sinus return), by intermittent aortic occlusion, aortic occlusion with elective arrest, or by discarding all blood removed from the open heart.

To minimize the risk of returning all blood removed from the open cardiotomy back into the main perfusion system, a coronary sinus system has been developed and used in 74 open heart operations. This system includes a foot pedal with variac control, operated by the second surgical assistant. He regulates the speed of the roller pump, thus controlling the amount of suction generated at the suction tip. In addition, the aspirated blood passes through an area of reduced velocity, a negative pressure zone, contact with defoaming agents, and blood filters. In short, this system has been designed to minimize the development of bubbles and foam manufactured at the suction tip, to allow any bubbles in the system to enlarge, rise, and rupture, and to contain the level of admixed blood and air. The filters are mainly used to remove muscle, calcium, and clots which may be aspirated from the operative field.

In 35 cases where complete data are available regarding all aspects of the perfusion, several thousand milliliters of blood in certain patients has been returned to the main perfusion system without apparent untoward effect.

Because of the rapid diffusibility of carbon dioxide, the layering of the operative field with this gas, utilized in only a few of the latter cases in this series, not only reduces the possibility of trapping air in the heart chambers, but also reduces markedly the opportunity for air bubbles to be manufactured at the suction tip.

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EXPERIMENTAL GAS GANGRENE: EFFECT OF CLOSTRIDIAL AND STAPHYLOCOCCAL TOXOIDS ON SURVIVAL TIME

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THE treatment of established gas gangrene is at best difficult. The surgical procedures required are generally formidable, and the conditions under which they are carried out often make them heroic. A profound toxemia is already present when the diagnosis is made, since the toxemia is a necessary element in the clinical diagnostic picture.[16]

Antibiotics or chemotherapeutic agents seldom suffice alone to control the progress of clinical gas gangrene, even though they appear to be effective against clostridial infection in small laboratory animals.[3, 4, 8, 9, 11] Likewise, antitoxin, which is clearly of value in some laboratories,[5, 8, 19, 26, 27] does not have an enthusiastic clinical acceptance,[10, 18, 20, 25] in spite of a few careful studies demonstrating a clinically useful effect.[17] The present-day incidence of gas gangrene is low. The record of the past indicates, however, that the incidence of the disease may rise markedly whenever conditions are such that prompt and adequate surgical treatment of wounds is not feasible. These are the reasons for interest in the development of active immunization against gas gangrene.

The interest understandably rises when the risk of wounding increases, and rises even more with any increase in the probability of a significant delay in optimum treatment of the wounds. The tactical use of atomic weapons on the battlefield may reasonably be expected to lead to a concentrated incidence of wounds, temporary saturation of medical treatment facilities, and isolation of units from their lines of communication. Strategic use of atomic weapons against urban areas would result in comparable situations in the civilian community. Gas gangrene may be a major threat in any future conflict.

From a technical standpoint, the development of active immunization against gas gangrene is in an advanced state. Toxins have been isolated and toxoids have been produced.[1, 2, 24, 29] The toxoids produce noteworthy rises in antitoxin titer in human subjects.[2] Comparable rises in antibody titer have been demonstrated to be of significant protective value in laboratory preparations.[2] However, this does not yet amount to a manifest case for the practical value of toxoid immunization, even in a high-risk population.

To date, most of the studies of protective value have been made on the guinea pig preparation of Altemeier.[2] This preparation is excellent for widespread laboratory use. It combines muscle damage, dirt, and a known and

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This article does not represent official opinions of the United States Army. Opinions expressed are solely those of the authors or of authorities cited in references.

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controllable organism. Nevertheless, the studies do not offer the optimum basis for extrapolation to experience with human beings. There are obvious discrepancies between the effectiveness of antibiotics and antitoxin in the guinea pig and other small animals, and the relative lack of effectiveness in human beings or in large animals. These discrepancies may be founded on considerations as simple as the relative sizes of the muscle masses involved, or the problem may be more intricate and more subtle, involving polymicrobic infection, associated shock, or metabolic differences.

It has recently been demonstrated that *Clostridium perfringens* infection of muscle is a major determinant of survival time in a massive, open experimental wound in the goat.[13, 14, 21] The goat preparation resembles the human clinical disease more closely than does any other laboratory preparation known to us. It has appeared of interest to us to use this preparation to assay the effects of perfringens toxoid on survival time.

The study was expanded to include the administration of *Staphylococcus aureus* toxoid, in view of various suggestions that staphylococcal infection might be of importance as an initiating or potentiating factor in clostridial infection of muscle.[7, 12, 23]

MATERIALS AND METHODS

Castrated male Texas Angora goats of the type used in previous studies from these laboratories were utilized. They were subjected to the standardized unilateral high-explosive wound of the thigh as described in previous publications.[13, 14, 22] Under the conditions of these studies, such wounds have been shown to be invariably lethal when untreated, with a mean survival time of approximately 25 hours. One of the major determinants of survival time has been shown by Lindsey and Noyes[13, 14, 21] to be the dosage of *Clostridium perfringens* to which the animals are exposed in the course of the naturally developing infection of the wounds.

The animals and method of wounding were as described previously,[22] with a few exceptions. In view of the extended period of time required for immunization prior to wounding, all animals were specially examined for general health before selection from the general input stream. Once selected, animals were assigned to experimental or control groups. Experimental groups were immunized according to the time and dosage schedule outlined in Table I. Both the *Clostridium perfringens* toxoid and the *Staphylococcus aureus* toxoid were supplied by Lederle Laboratories. All goats received a single intramuscular injection of penicillin immediately after wounding (0.6 Gm. crystalline penicillin potassium, and 0.2 Gm. procaine penicillin).

Because of the limitations on wounding and holding facilities, and the complexity of the immunization schedules, experimental groups were scheduled, wounded, and studied in series rather than in parallel (that is, effect of day and treatment were confounded). However, all wounding was accomplished within a span of 17 calendar days. Laboratory personnel who cared for the animals, took samples, and made laboratory determinations were not aware of the particular group under study at a given time.

TABLE I. SCHEDULE FOR INJECTIONS OF GOAT GROUPS WITH TOXOIDS

GROUP NO. AND DESCRIPTION	INJECTION	DAY	NO. OF ANIMALS	ROUTE OF ADMINISTRATION	DOSE (ML.)	REMARKS
Cl. perfringens, staphylococcus, and adjuvant*	1st	0	5	i.m.	40	5 ml. given in each of 8 sites
	2nd	7	5	i.m.	40	5 ml. given in each of 8 sites
	3rd	21	5	i.v.	2	Staphylococcus and perfringens toxoid only (1 ml. each)
	—	35	5	—	—	Wounded
Staphylococcus toxoid	1st	0	10	i.v.	0.8	
	2nd	14	10	i.v.	0.8	
	3rd	28	10	i.v.	0.8	
	—	35	10	—	—	Wounded
Cl. perfringens toxoid	1st	0	10	i.v.	2.8	
	2nd	14	10	i.v.	2.8	
	3rd	28	10	i.v.	2.8	
	—	35	10	—	—	Wounded
Cl. perfringens and staphylococcus toxoid	1st	0	10	i.v.	2.8	Perfringens toxoid
	2nd	7	10	i.v.	1.6	Staphylococcus toxoid
	3rd	14	10	i.v.	4.4	Mixed as above dose
	4th	28	10	i.v.	4.4	Mixed as above dose
	—	35	10	—	—	Wounded

*Formula for *Cl. perfringens*, staphylococcus toxoids, and adjuvant:

First injection — 22.5 ml. *Cl. perfringens* toxoid, 10.5 ml. staphylococcus toxoid, 58.0 ml. normal saline, 86.0 ml. Bayol, 44.0 ml. Falba, 86.0 mg. *M. tuberculosis* bacilli, all homogenized in a blender.

Second injection — same formula as first, without the *M. tuberculosis* bacilli.

RESULTS

In one control group, 4 of the 8 animals died without accurate determination of survival times. This group is therefore omitted from the evaluation.

A study of the 36-hour survival times is of interest. Thirty-six hours after being wounded most of the control animals usually have died. After 36 hours, detrimental effects of immobilization may become a factor contributing to the death of the animals.

It will be noted (Fig. 1 and Table II) that 100 per cent (5/5) of the goats immunized with *Cl. perfringens* toxoid, staphylococcus toxoid, and adjuvant lived over 36 hours. Of the animals receiving *Cl. perfringens* and staphylococcus toxoid immunization 77.8 per cent (7/9) lived over 36 hours. Seventy per cent (7/10) of animals receiving *Cl. perfringens* toxoid alone survived over 36 hours. Thus a total of 19/24 (78.7 per cent) of animals immunized with *Cl. perfringens* toxoid alone or in combination lived at least 36 hours.

In comparison with this group, no untreated animals survived 36 hours (0/5). One control group receiving only penicillin yielded two 36-hour survivors out of 5 animals (40 per cent). In a second control group, also receiving only penicillin, 2 of 5 animals were 36-hour survivors. Thus there were 4/10 (40 per cent) total 36-hour survivors in those receiving penicillin alone. Of the 10 animals receiving staphylococcus toxoid only 3 lived over 36 hours (30 per cent). It is interesting to note that of the 25 animals receiving no *Cl. perfringens* immunization, only 3 lived over 50 hours. These animals did

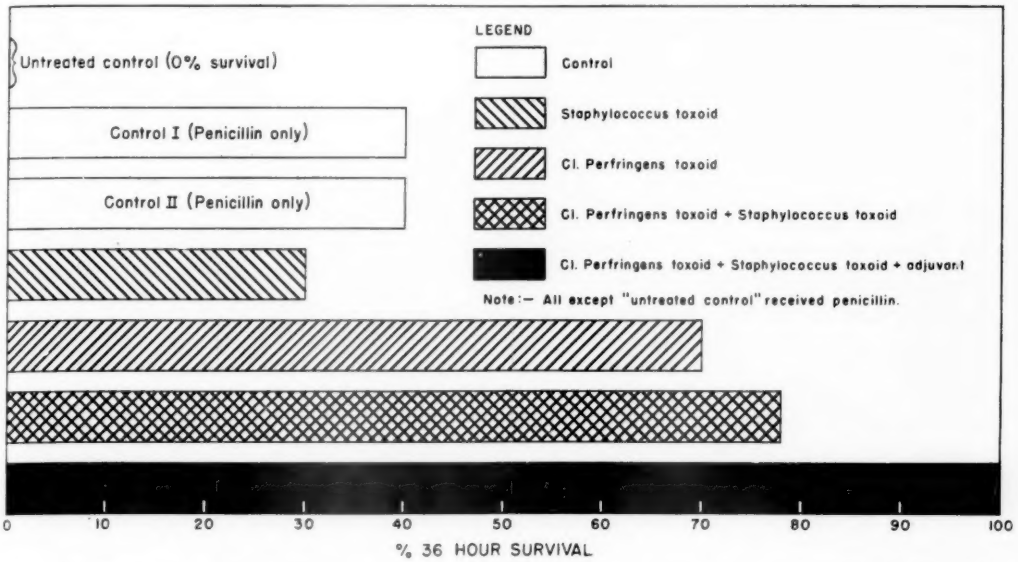

Fig. 1.—Effect of immunization on survival time (per cent of animals surviving beyond 36 hours).

receive intramuscular penicillin. In contrast, 10 of the 24 goats receiving perfringens immunization alone or in combination survived over 50 hours.

Although it appears from these figures that the addition of the adjuvant was of considerable benefit, the difference is not actually mathematically significant. The probit graph (Fig. 2) illustrates that although there is a significant difference in rate of death between all animals immunized with perfringens toxoid and all of those that did not receive it, the differences among the individual components of these 2 large groups are not significant.

TABLE II

TREATMENT	SURVIVAL TIME (HR.) MEAN	RANGE	MEDIAN	36-HOUR SURVIVAL NO.	%	MEAN CLOSTRIDIUM COUNT (16 HR., LOG 10)	MEAN STAPHYLOCOCCUS COUNT (16 HR., LOG 10)
Cl. perfringens, staphylococcus toxoid, and adjuvant	51.60	36.83-72.08	46.3	5/5	100	6.0	3.8
Control for *Cl. pefringens*, staphylococcus toxoid, and adjuvant	34.39	20.66-52.50	28.5	2/5	40	5.4	3.0
Staphylococcus toxoid	31.37	15.16-56.75	27.0	3/10	30	6.1	3.6
Cl. perfringens toxoid	45.09	34.00-60.55	42.7	7/10	70	5.0	4.7
Cl. perfringens and staphylococcus toxoid	46.76	32.13-59.55	44.4	7/9	77.8	5.4	3.0
Controls with penicillin	38.67	7.42-85.08	22.5	2/5	40	4.6	4.2
Controls without penicillin	26.83	21.33-30.87	25.2	0/5	00	6.6	2.4

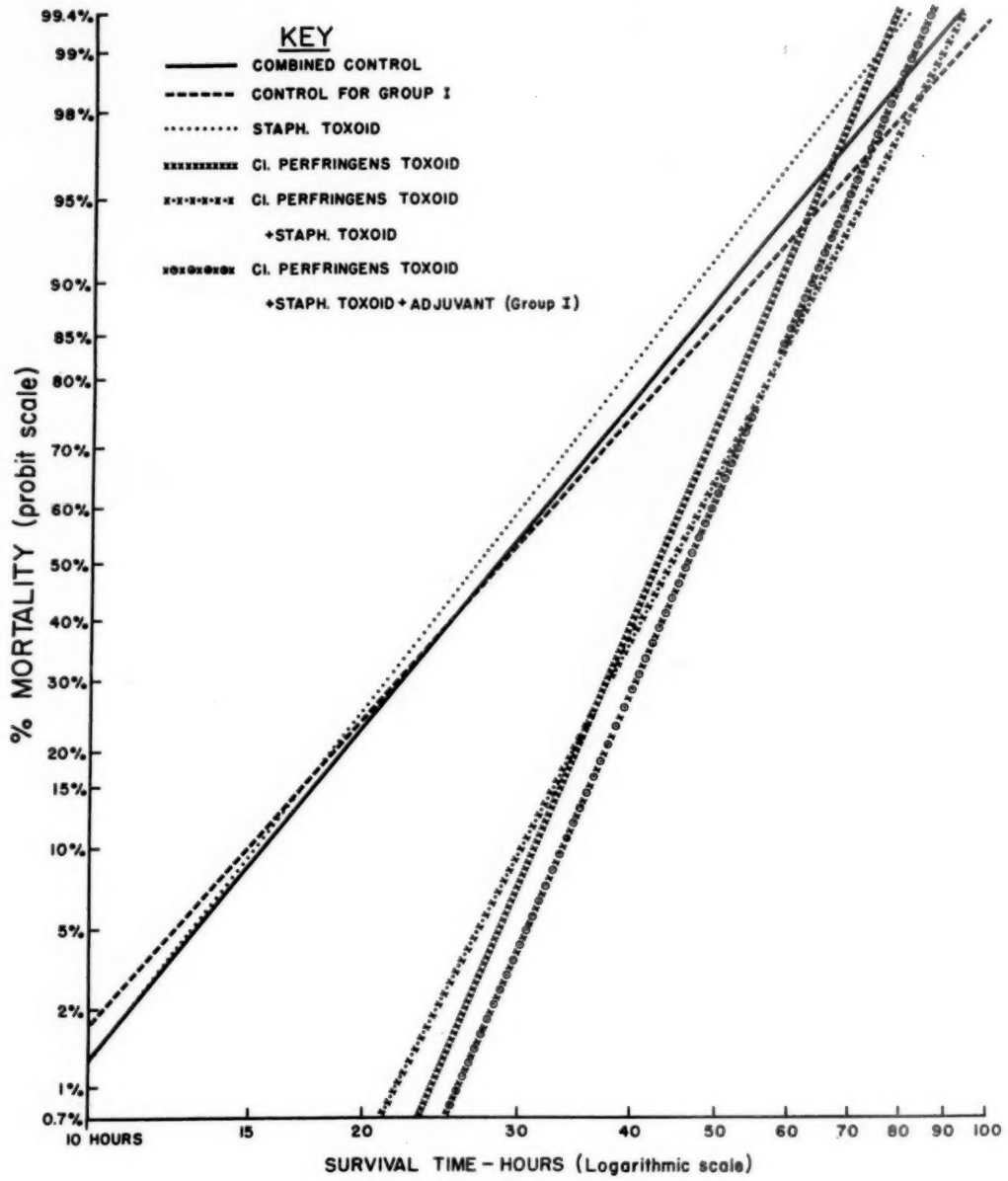

Fig. 2.—Effect of immunization on survival time (probit slopes).

Statistical analysis of this work was carried out and given in the following report by Dr. J. C. Atkinson, with a coding system to simplify comparisons.

Coding System.—

Group I: Goats immunized with *Cl. perfringens* toxoid, staphylococcus toxoid, and adjuvant (treated with penicillin).

Group IC: Penicillin-treated unimmunized goats studied simultaneously with Group I (control for Group I).

Group II: Penicillin-treated goats immunized with staphylococcus toxoid only.

Group III: Goats immunized with *Cl. perfringens* toxoid only (treated with penicillin).

Group IV: Unimmunized penicillin-treated goats serving as controls, but used on a different day. (Omitted from analysis because exact survival time of 4 of the 8 animals not known.)

Group V: Goats immunized with *Cl. perfringens* toxoid and staphylococcus toxoid (penicillin-treated).

Group VIA: Unimmunized penicillin-treated goats serving as controls.

Group VIB: Unimmunized goats receiving no penicillin (untreated control).

Combined Control: Group IC and Group VIA.

Method of Analysis.—Regression equations for probit per cent mortality rate (y) were fitted in terms of log survival time (x). The method of Bliss[6] was used. An analysis of variance about the line was conducted in terms of y (probit per cent death). From this the variance of x was estimated as in dosage mortality rate curves[6] at the 50 per cent survival point for each curve. The variances were appropriately combined to produce least significant differences among the 50 per cent survival time estimates. One hundred per cent mortality rates occurred in all groups. The slopes of Group IC and Group VIA were shown to be not different. This was used as a justification in pooling them into the "combined control."

Conclusions.—The times to 50 per cent survival (median survival time) are given in Table II. Statistically significant increases in 50 per cent survival times were demonstrated for Groups I, III, and V over the combined control. Group I had a significantly longer median survival time than the Group I control.

Antitoxin assays were performed on some of the sera.* Sixteen of the 19 specimens tested had high staphylococcus titers (at least 16 U. per milliliter).

The highest *Cl. perfringens* antitoxin titer reported (between 1.6 and 3.2) occurred in a goat immunized with *Cl. perfringens* toxoid and adjuvant, although some of this group showed less than 0.4 U. It is, of course, theoretically possible that a titer less than 0.4 U. may be protective. Unfortunately, in the method used, titration below 0.4 U. was not possible.

Of the control animals tested, 5/5 had titers less than 0.4. Thus it appears that there was no high level of antitoxin before immunization and that an increase in the level was reached in at least some animals by immunization. However, the small number tested and the absence of titrations below the level of 0.4 U. does not permit these results to be considered an adequate evaluation of the degree of circulating antitoxin obtained. These results are summarized in Table III.

DISCUSSION

It must be recalled that these animals with massive wounds received no treatment other than that specifically stated. No parenteral fluids were given and no local wound care was provided beyond initial hemostasis and gauze dressing. The animals were restrained on carts in a prone position, which is a

*Assays were performed by Lederle Laboratories, Biological Control Laboratory, Miss Frances L. Clapp, director.

TABLE III. CL. PERFRINGENS ANTITOXIN ASSAYS

IMMUNIZATION GROUP	*Cl. perfringens* ANTITOXIN (U./ML.)	
	LESS THAN 0.4	OVER 0.4
I. Perfringens, staphylococcus, and adjuvant	2/4 (Retest: 1/4)	2/4 (Retest: 3/4)*
IC. Control for Group I	5/5	0/5
V. Perfringens and staphylococcus	4/9 (Retest: 5/9)	5/9 (Retest: 4/9)

*One sample was reported as 0.8 U. per milliliter on the first test and between 1.6 and 3.26 U. per milliliter on retest. All of the other samples were less than 0.8 U. per milliliter.

position known to be detrimental to ruminants in general. The measurable circulating antibody level was raised only moderately. Thus any benefit derived from the therapy under study probably represents the minimum. It is indeed possible that with supplemental care the beneficial effects could be far more apparent.

It is evident that toxoid immunization does not result in any significant depression of the mean bacterial count (Table II). This is not unexpected. Both of the toxoids are known to be potent antigens and immunity produced is antitoxic, not antibacterial. It is possible to conceive of an effect on bacterial concentration (particularly of *Cl. perfringens*) which would be the result of such antitoxic actions as the blocking of invasion and tissue breakdown, and the prevention of the conversion of living or freshly dead tissue into an optimum pabulum for growth.

Immunization with staphylococcal toxoid apparently has no significant effect on survival time. This result comes as no particular surprise. Mixed infection is the rule in gas gangrene, but there have been few pointed inferences that the role of any one aerobe is causal rather than casual.

In spite of the deficiencies of the data on mean survival time, the analysis of the data by probit slope (Fig. 2) clearly shows the internal consistency of the various groups of animals, and indicates, with an acceptable degree of statistical significance, that perfringens toxoid does have an effect in prolonging survival time, while staphylococcal toxoid does not. Although perfringens-immunized animals show a wide range of survival times, with some animals dying as early as unimmunized animals, the rate at which perfringens-immunized animals die (the slope of the mortality rate plot) is significantly slower. If we consider only the point at which 50 per cent of the animals in a series are dead and 50 per cent alive (the most accurate point on these curves), it is evident that perfringens immunization has delayed death by a factor of some 15 to 20 hours. This effect is also shown when the survival time of the individual animal is plotted (Fig. 3).

That perfringens immunization is totally ineffective in terms of the ultimate mortality rate is quite clear. All of the animals finally died. However, this ineffectiveness in terms of the ultimate mortality rate does not necessarily militate against the practical value of a potential clostridial vaccine. It is a wild hope to hypothesize an effective treatment of established gas gangrene which does not include major operative procedures. One cannot seriously expect

an immunization of any sort to protect consistently against an overwhelming parenteral injection of virulent organisms, such as is the circumstance in massive, open, and dirty wounds resulting from violence.

We have no data as yet to support the hope that the 15 to 20 hour delay in the probit mortality rate is a general delay in the biologic process. If, for example, this represents not only a prolongation of survival, but also a prolongation in the "golden period" before definitive surgery, then a clostridial vaccine would be well worth using. It might permit us to save as many as 50 per cent of the patients whose definitive operation is necessarily delayed for 18 to 24 hours after wounding.

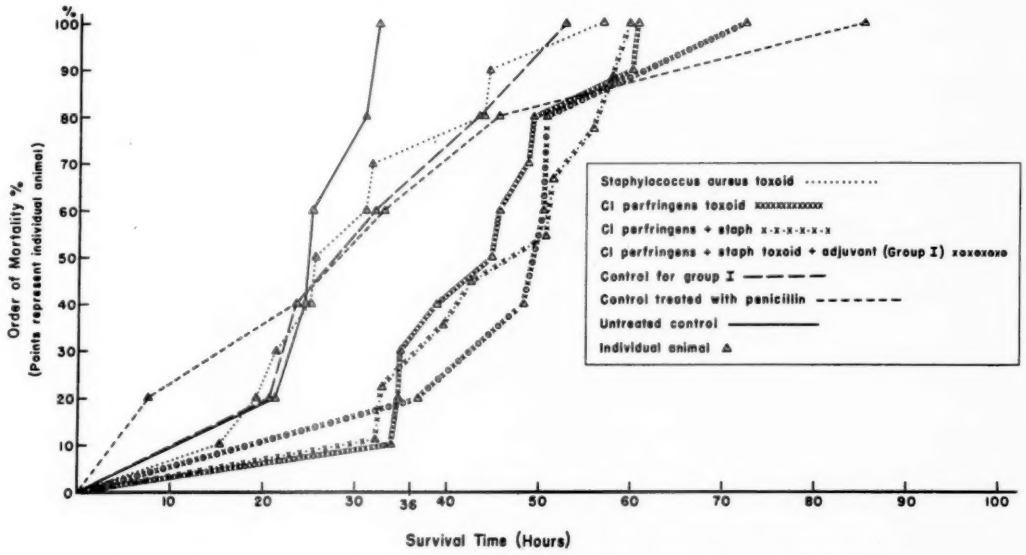

Fig. 3.—Effect of active immunization on survival time (individual animals).

CONCLUSION

In a standardized experimental hindquarter wound, in which clostridial infection is a major determinant of survival time, immunization with *Cl. perfringens* toxoid produces a statistically significant prolongation of survival. The clinical value of this prolongation has not been established. Immunization with staphylococcal toxoid is without apparent effect.

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Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

APPENDICITIS DURING THE FIRST MONTH OF LIFE

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APPENDICITIS during the first month of life is rare.[1-37] Fields and associates[13] reported 5,354 operations for acute appendicitis for the years 1942 to 1952 at the Los Angeles County Hospital. Thirty-eight of the patients were under 3 years of age, and only 1 was under 1 month of age. Other large series reported by Nassan[27] (465 cases), Abel[1] (1,165 cases), Deaver[9] (777 cases), Hudson[16] (848 cases), McLaughlin[21] (300 cases), Meagher[23] (405 cases), Penberthy[29] (1,653 cases), Scott[33] (506 cases), and Snyder[35] (1,051 cases) did not include any patients under 1 month of age. Inasmuch as only 19 cases have been reported to date (Aug. 15, 1959), the occurrence of 5 within a 7-year period in one geographic area seemed worthy of notation. The diagnosis was unsuspected in each instance, and the mortality rate was 100 per cent. It was believed that details of the clinical findings in our patients, as well as those reported in the literature, may be helpful in the recognition of this disorder in the young infant.

CASE REPORTS

CASE 1.—A 14-day-old white male weighing 9 pounds, 5 ounces (4.2 kilograms), at birth developed mild diarrhea (2 to 3 loose stools) on the tenth day of life followed by refusal of food. There was no vomiting. Change in type of feeding was not helpful, but at frequent intervals he took small amounts of water. Thirty-six hours after onset of symptoms, when the patient was first seen by a physician, the temperature was 101° F. and the heart rate was rapid. Marked irritability of the infant made examination very difficult, but the abdomen did not appear to be distended or rigid. Peristalis was heard. Results of rectal examination were normal, and no other evidences of disease were elicited. There were no further bowel movements. Twelve hours before death the infant took 2 ounces of a thin milk mixture, and retained a small amount of water. During the day he was restless, yet lethargic. Suddenly he turned blue and was taken immediately to the emergency hospital where he was pronounced dead on arrival. Autopsy findings of significance were confined to the abdomen. In the peritoneal cavity there was approximately 2 ounces of fibrinous exudate. The loops of the small intestine were intimately bound together by fibrinous adhesions but were easily separated. The most intense inflammatory reaction was along the right gutter. A small, markedly distorted, acutely inflamed appendix was identified, and gentle pressure near the tip produced purulent material from a minute perforation. Cultures revealed *Escherichia coli* and nonhemolytic *Staphylococcus albus.*

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CASE 2.—On the fifteenth day of life, a white female infant had become irritable yet placid and had had episodes of pallor and lethargy associated with some shortness of breath. There was no vomiting but she ate poorly. She was admitted to the hospital the next day. The temperature was 99° F. and the heart rate was rapid. She appeared to be well developed and nourished, was quite alert, and had a strong cry. Slight cyanosis was the only suggestive clinical finding other than a slightly distended abdomen. No masses or evidences of tenderness could be elicited. The hemoglobin was 24.6 Gm., and leukocyte count 23,500. Urinalysis gave negative results. Pneumonia or atelectasis was suspected, and the infant was placed in oxygen and given penicillin and streptomycin. Her condition grew rapidly worse. Terminally the abdomen became quite distended. She died 8 hours after admission, at which time some discoloration of the abdominal wall was noted in the right lower quadrant. At autopsy there were patchy areas of consolidation in the lungs. The abdomen was distended and when it was opened a thick exudate was found, particularly in the region of the ileocecal valve. The appendix was perforated.

CASE 3.—A 16-day-old male infant refused his feeding, vomited, and had 2 greenish, loose bowel movements. He was admitted to the hospital. The temperature was found to be 96.4° F. The infant appeared thin, dehydrated, and in generally poor condition. The abdomen was markedly distended and firm and no peristalis was heard. The abdominal wall was edematous. Nasogastric suction was instituted after which the upper abdomen became soft, but the lower remained tense and firm, especially in the right lower quadrant. Roentgenograms of the abdomen taken in the upright and supine positions showed large amounts of air in the stomach and moderate distention of the small bowel and even to the rectum. Fluid levels could not be seen, and the loops were separated in a manner which suggested fluid in the peritoneal cavity. The hemoglobin was 23 Gm. and the leukocyte count 31,500. The tentative diagnosis of peritonitis secondary to a perforated appendix was offered. Therapy consisted of intravenous fluids, oxytetracycline hydrochloride, and nasogastric suction. The infant's condition rapidly deteriorated and he died 6 hours after admission. Autopsy revealed an edematous abdominal wall, about 200 c.c. of purulent fluid within the peritoneal cavity, loops of bowel matted together by an organized fibropurulent exudate, several lobules of pus in the region of the cecum, and a tortuous appendix with a necrotic tip with perforation.

CASE 4.—An 8-day-old premature male infant with a birth weight of 3 pounds, 3 ounces (1,450 grams), had been having a difficult time from the beginning, but his condition had seemed quite satisfactory until the day of death. Respiratory efforts became gaspy, he vomited once, and had a bowel movement. He appeared to be in poor condition with definite cyanosis and mild abdominal distention. His condition rapidly deteriorated. Autopsy revealed many dilated intestinal loops with a fibrinous exudate. A perforated appendix sharply kinked on itself was found in the paracolic gutter.

CASE 5.—A 19-day-old white female infant had been progressing normally. The day before admission, she had become irritable and had vomited after the evening meal. The same day, she had had 2 normal bowel movements. Suddenly the infant had become limp and was brought to the emergency hospital in a moribund condition. She died within 15 minutes. Autopsy examination showed a distended abdomen and intestinal loops tightly bound down by fibrinous adhesions. The appendix was gangrenous with evidence of perforation at the distal portion. When the cecum was opened, a tumorlike mass could be seen in the region of the terminal ileum which caused obliteration of the appendical lumen. This mass proved to be ectopic pancreatic tissue on histologic examination.

In order to provide a review of such factors as age, sex, symptomatology, autopsy (or operation) findings, and results pertaining to the 19 reported cases (1900 to 1959), summary data are presented in Table I. Included in this table are the findings concerning the 5 infants cited in this paper.

Of the 24 infants with appendicitis, 4 were premature, and the ages varied from 1 to 21 days. Males predominated over females approximately 3 to 1. The first instance was reported in 1908 and the next in 1912, while 9 of the first 19 cases were reported from 1949 to 1959. The symptomatology and manifestations were indicated for 22 infants. Vomiting was present in 15, refusal of feedings in 6, evidence of pain (crying, colic, or irritability) in 5, listlessness in 4, loose stools in 3, constipation in 5, abdominal distention in 15 with evidence of tenderness and rigidity in 3, fever in 2, and convulsions in 2. Peritonitis was present in 19. Operation was performed on 7 infants. Four infants recovered, in all of whom the appendix was not ruptured.

DISCUSSION

It is well known that in small infants the symptomatology of meningitis may be so obscure that the diagnosis is made only after spinal fluid is obtained for study. This vagueness of signs and symptoms typifies many other conditions such as sepsis. Certainly it is apparent from the review of the histories of infants with appendicitis in the first month of life that diagnosis is extremely difficult. It would appear that in infants with vomiting and/or loss of appetite, in whom there is a suggestion of abdominal distention, the possibility of appendical inflammation should be considered. Symptoms suggesting pain (colic, irritability, crying) may occur. Other clinical features such as diarrhea or constipation, fever, listlessness, or even convulsions may be present but are too nonspecific to lead to the diagnosis. The clinical course of the disease may be rapid with death following 24 hours after onset of recognized symptoms. This is especially true with premature infants. Examination of the abdomen must be performed with extreme lightness of touch and patience. Localized tenderness is unusual and the elicitation of any abdominal tenderness will depend upon close observation of the infant for evidences of distress during gentle palpation. In any situation when an "acute abdomen" is suspected the possibility of appendicitis must be considered.

Inasmuch as obstruction of the appendicial lumen is believed to be conducive to an acute inflammation, the question arises concerning the likelihood of obstruction of the lumen during the first month of life. The great amount of lymphoid tissue in the appendix in early life may be significant. Obvious kinking of the appendix occurred in 2 of our cases. In addition, aberrant pancreatic tissue in a third instance led to obstruction of the lumen of the appendix.

The younger the child, the earlier the likelihood of rupture of an acutely inflamed appendix. Hence it is no wonder that peritonitis was present in most of the infants. The absence of even a relatively short period when localized signs may be elicited explains the difficulty in diagnosis of the acutely inflamed appendix during the first months of life.

SUMMARY

1. Five deaths from appendicitis in infants less than 1 month of age occurred in one geographical area during a 7-year interval. It would appear that appendicitis in the first month of life is more common than has been suspected.

TABLE I. CASE REPORTS OF APPENDICITIS IN THE FIRST MONTH OF LIFE IN THE LITERATURE FROM 1900 TO 1960

SOURCE	TOTAL DURATION OF ILLNESS (DAYS)	AGE (DAYS)	SEX	YEAR	SYMPTOMS	OPERATION OR AUTOPSY FINDINGS	RESULT
Etherington-Wilson[12]	4	16	M	1945	Refused feedings, vomiting, persistent crying, distention, constipation	Gangrenous distal half, generalized peritonitis, operation	Died
John[17]	4	21	M	1936	Vomiting, listlessness, mild melena, no abdominal signs	Autopsy, perforated tip, generalized peritonitis	Died
Hill[15]	3	3	F	1925	Vomiting, distention	Autopsy, perforated appendix, generalized peritonitis	Died
Corcoran[8]	2	3	M	1930	Convulsions, no abdominal findings, hydrocele	Autopsy, ruptured appendix, generalized peritonitis, empyema right chest	Died
Lipshutz[19]	1	1	—	1931	Not given	Autopsy, gangrenous appendix, no perforation	Died
Diess[10]	8	14	M	1908	Vomiting, distention, otitis media	Operation, acute appendicitis, diffuse peritonitis	Died
Canaguier[4]	5	5	M	1912	Vomiting, distention obstipation	Operation, acute appendicitis, generalized peritonitis	Died after evisceration 10 days postoperatively
Krock[18]	4	21	M	1935	Restlessness, colic, vomiting	Operation, ruptured appendix, generalized peritonitis	Died
Ch'eng[5]	9	3	M	1937	Refused feedings, distention, constipation	Autopsy, acute appendicitis, generalized peritonitis	Died
Engstrom[11]	6	21	M	1949	1,290 grams, premature	Autopsy, acute appendicitis, generalized periotonitis	Died
Meyer[25]	4	9	F	1952	3 pounds, 9 ounces, premature, vomiting	Autopsy, gangrenous appendix, generalized peritonitis	Died
Meigher[24]	2	10	F	1952	Irritable, refused feedings, abdominal distention	Operation, acute appendicitis, no perforation	Recovered

Riddell[32]	2	15 (premature)	M	1954	Fever, vomiting, abdominal distention, rigidity	Operation, gangrenous appendix	Recovered
Baker[3]	8	5	M	1954	Vomiting, diarrhea, obstipation, abdominal distention	Operation, gangrenous thin-walled unruptured appendix	Recovered
Fields[13]	2	15	M	1957	Restlessness, irritability, refused feedings, abdomen distended and tender	Operation, acute appendicitis	Recovered
Shinaberger[34]	4	15	F	1958	Vomiting, constipation, cellulitis right flank	Autopsy, diffuse peritonitis, ruptured retrocecal appendix	Died
Walker[37]	1	5 (premature)	F	1958	Listlessness, anorexia, abdomen doughy	Autopsy, diffuse peritonitis, ruptured appendix	Died
Walker[37]	1	1 (premature)	F	1958	Ate poorly, apneic, abdomen firm	Autopsy, diffuse peritonitis, ruptured appendix	Died
Coetzee[7]	4	9	M	1958	Constipation, vomiting, abdominal distention, dehydration	Autopsy, diffuse peritonitis, ruptured appendix	Died
Authors	4	14	M	1960	Diarrhea, anorexia, no vomiting, fever, apathy, abdominal distention	Autopsy, diffuse peritonitis, perforated appendix	Died
Authors	1	16	F	1960	Irritable, lethargic, anorexia, no vomiting, abdominal distention	Autopsy, diffuse peritonitis, ruptured appendix	Died
Authors	1	8 (premature)	M	1960	Vomiting, abdominal distention	Autopsy, diffuse peritonitis, ruptured appendix	Died
Authors	1	19	F	1960	Irritable, vomiting, abdominal distention	Autopsy, diffuse peritonitis, ruptured appendix	Died
Authors	1	16	M	1960	Vomiting, diarrhea, abdominal distention, x-ray abdomen and ileus	Autopsy, diffuse peritonitis, ruptured appendix	Died

2. To date only 19 instances have been reported in the literature.

3. On the basis of personal and reported experience it is apparent that appendicitis in this period of life is extremely difficult to diagnose, and that once perforation has occurred (83 per cent of the patients) the outcome has been fatal.

4. In the 4 reported cases of patients who recovered, operation had been performed before perforation.

5. The symptomatology of appendicitis during the first month of life is extremely obscure, but the possibility of this condition should be considered in every infant with signs which might indicate an acute abdominal condition. Abdominal distention and vomiting were the 2 most common findings. A plain film of the abdomen with evidences of ileus and separation of intestinal loops may be helpful in the diagnosis. Such features as refusal of feedings and evidence of pain (colic, crying, irritability), observed in one-fourth of the patients, may be helpful in the establishment of early diagnosis. Localized signs, rectal examination, and leukocyte count have been of no assistance. The only solution is early operation.

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MECONIUM PERITONITIS SECONDARY TO INTESTINAL ATRESIA

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CONGENITAL atresia of the intestine is a rare anomaly occurring in approximately 1 of every 1,500 infants born.[13] If an infant born with intestinal atresia is not treated by decompression of the bowel, the intestine continues to dilate and perforation from ischemic necrosis usually takes place. Peritonitis and death result.[19]

Occasionally the perforation of the intestine occurs in intrauterine life, allowing meconium to pass into the peritoneal cavity. This results in a sterile chemical and foreign-body peritonitis known as meconium peritonitis.[6]

Meconium peritonitis is seldom encountered. By 1949, Low[22] was able to find only a few more than 100 cases in the medical literature. Bendel and Michel[4] reported only 3 cases diagnosed at Charity Hospital in New Orleans over a 15-year period during which 108,744 live births had been recorded.

Meconium peritonitis is most frequently caused by a perforation proximal to the site of intestinal atresia.[27] Another reported cause is intestinal obstruction due to internal hernias, volvulus, congenital bands, and meconium ileus.[1] Cases have also been reported in patients without intestinal obstruction, some of whom have had fibrocystic disease of the pancreas.[31, 33]

Our report concerns an infant with meconium peritonitis secondary to intestinal atresia, successfully treated with a 4-year follow-up.

CASE REPORT

B. D., a white female infant, was born at The Long Island Jewish Hospital on Jan. 8, 1956, and weighed 5 pounds, 14 ounces. Some vomiting was reported in the first 2 days of life and it increased on the third day. One meconium stool a day was noted during this period. On January 11, bile-stained vomitus and abdominal distention were observed. X-ray studies of the abdomen demonstrated distended loops of bowel on the left side and a mottled gas and fluid shadow on the right. Some flecks of calcification were also noted (Fig. 1). The diagnosis was intestinal obstruction with associated meconium peritonitis.

The abdomen was opened with a transverse incision, one finger breadth above the umbilicus and across both recti. There was no free air in the peritoneal cavity. Extensive adhesions were found between the loops of bowel. There were several small yellow masses found scattered in the peritoneal cavity. The first 2 cm. of intestine retrograde from the ileocecal valve was collapsed, but was otherwise normal. This segment was succeeded by a 10 cm. segment, atretic at both ends and twisted on itself around an adhesive band which was attached at its other end to the right broad ligament. Proximal to the atretic segment, the small intestine was markedly distended and cyanotic for 25 cm. The remaining proximal jejunal loops were completely bound down by adhesions, but were otherwise normal. The site of previous perforation could not be identified. The colon was completely collapsed and empty, but was normal. The distal 25 cm. of dilated ileum

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were resected along with the segment atretic at both ends (Fig. 2). The proximal end of the ileum was then closed in 2 layers with an inverting stitch of No. 4-0 chromic catgut followed by interrupted No. 4-0 silk sutures. The distal ileum and cecum were inflated with saline and a side-to-side ileoileostomy was carried out with an inner layer of No. 4-0

Fig. 1.—Preoperative film of erect abdomen showing intestinal distention and fluid levels.

Fig. 2.—Unopened resected specimen. Note the marked distention and twisted atretic segment in lower right.

chromic sutures and outer layer of interrupted No. 4-0 black silk sutures. The abdomen was closed in layers without drainage. The infant received 50 c.c. of whole blood during the procedure. The following pathology report was made by Dr. James Berkman.

Gross Description.—The specimen, which was received unfixed, consisted of 2 segments of small intestine, the serosal surfaces of which were interconnected by a wide band of fibrous tissue. The proximal segment was 25 cm. in length and was markedly distended, varying in diameter from 2 cm. at its proximal resected end to 3.8 cm. at its distal extremity,

which ended blindly (Fig. 3). It was connected to a twisted, collapsed second segment of intestine by a band of fibrous tissue approximately 5 cm. proximal to the blind end. The twisted segment was coiled upon itself. On being untwisted, it was found to be 10 cm. in length and varied from 0.8 cm. to 1.2 cm. in diameter. All serosal surfaces were covered by fibrous tags. The lumen of the distal segment contained semisolid, dirty gray-green material. Intercommunication between lumina could not be demonstrated. In the proximal portion of the distal twisted segment was a deeply hemorrhagic area. At no point in either the proximal or distal loop was a point of free perforation found. In the blind segment, the mucosa was flattened. In the twisted segment it was granular in appearance.

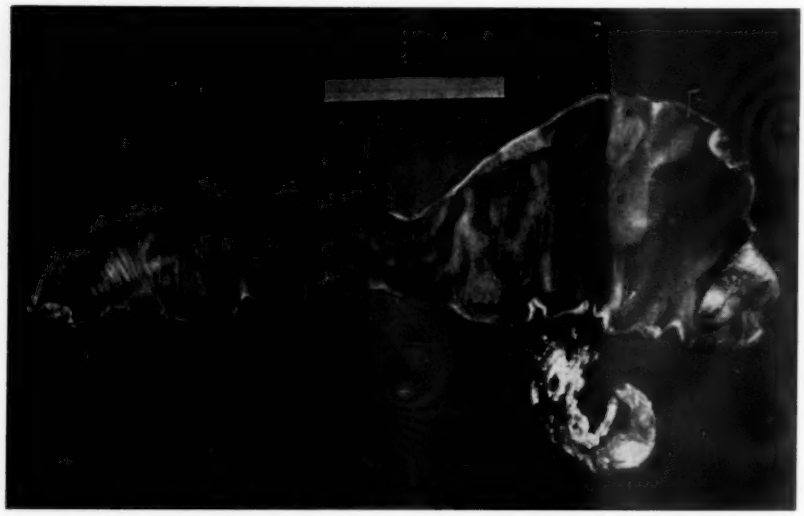

Fig. 3.—Opened resected specimen with marked flattening of mucosa and thinning of wall.

Microscopic.—Sections from the blind loop revealed a flattened but otherwise intact mucosa. The muscle coats were hypertrophied. The serosa was covered by vascular fibrous tags. In the collapsed twisted segment the mucosa was absent and was replaced by a conglomeration of calcific debris, foamy macrophages, and numerous foreign-body giant cells, some of which engulfed cornified cells. Similar calcific deposits, foreign-body giant cells, and cornified cellular debris replaced focal areas of submucosa, muscular coats, and serosa (Fig. 4). In one area all layers of the wall were reduced to a zone of dense fibrous tissue. The interconnecting band consisted of highly vascular fibrous tissue. It did not include usual elements of intestinal wall.

Pathologic Diagnosis.—The findings were diagnosed as a segment of ileum including blind loop proximal to the zone of congenital atresia and a collapsed, twisted distal atretic loop, dilatation and hypertrophy of the proximal loop, and healed perforation of the distal loop with meconium peritonitis.

Postoperatively, the infant was treated with intravenous fluids, gastric suction, and antibiotics. The baby had 2 bowel movements on the third postoperative day and was started on oral fluids. She then began to pass 10 to 15 stools per 24 hours, despite many changes of formula. Her weight gradually fell to a low point of 4 pounds, 14½ ounces on the twelfth postoperative day. Another transfusion of 50 c.c. of whole blood, as well as several clyses, were necessary. The stools then decreased to 5 to 7 per day and the infant's weight increased to 5 pounds, 7½ ounces at the time of discharge, 24 days after the operation. Blood chemistries remained normal despite the frequent bowel movements.

Five days later, the patient was readmitted because of a recurrence of the diarrhea. She was treated with intravenous fluids and then started on an alacta formula with additional cereal and banana. The baby's weight increased to 6 pounds, 11 ounces by the time of discharge 31 days later.

The baby was readmitted at 6 months of age because of vomiting of 1 day's duration. Her weight was 13 pounds, 4½ ounces. The child was treated with intravenous fluids for 24 hours. There was no further vomiting. She was started back on formula, remained asymptomatic and was discharged after 3 days of hospitalization.

Her last admission was at the age of 16½ months for diarrhea of 5 days' duration. Her weight was 20 pounds. She was treated with a diet of skimmed milk and bananas. A gastrointestinal series showed a normal pattern of small bowel at 30 minutes and passage of barium into the colon at 90 minutes. The bowel movements decreased to 4 to 6 per day and the patient was discharged after 4 days of hospitalization. She had learned to sit up at 6 months, walk at 1 year, and talk at 16 months.

At present, the patient is a well-developed, well-nourished child of 4 years, who weighs 33 pounds.

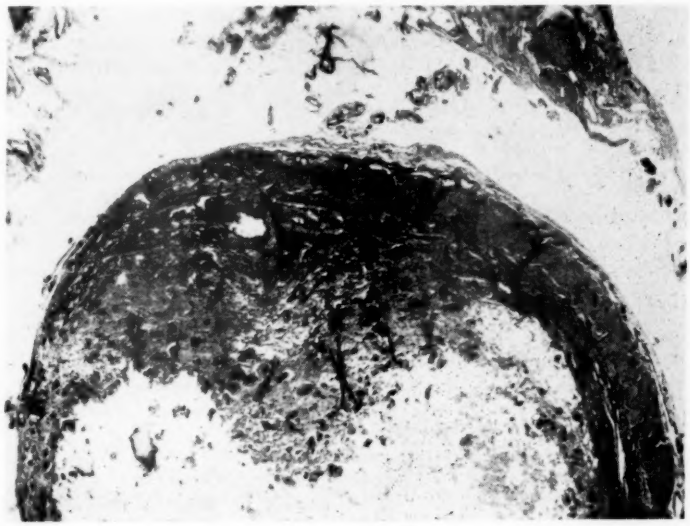

Fig. 4.—Microscopic section which shows calcific deposits and foreign-body giant cells in ileal wall.

DISCUSSION

The newborn infant with meconium peritonitis presents the picture of intestinal obstruction. Since the site of perforation has usually sealed over, the infant at birth frequently does not show signs of peritonitis. Vomiting occurs early and is usually bile-stained, for most atresias are distal to the ampulla of Vater. If the site of obstruction is low in the small intestine, abdominal distention develops. These findings indicate the need for x-ray studies of the abdomen. Roentgenograms show dilated intestinal loops proximal to the site of obstruction and scattered calcifications diagnostic of meconium peritonitis.[25, 30]

The infant should be prepared for operation by intestinal decompression with a nasogastric tube and hydration with parenteral fluids via a cut-down. The surgical treatment is complicated by the many dense adhesions resulting from the prenatal peritonitis. Dissection must be continued until the point of obstruction is found. This area can then be resected or bypassed to re-establish continuity of the bowel.

Survivors of the operation are uncommon. In 1943, the first successes were reported in patients who had meconium peritonitis, with and without intestinal

obstruction.[2] To date, there have been 11 survivors in the group with intestinal atresia (Table I), 9 in the group with other types of obstruction (Table II), and 11 in the group without any demonstrable obstruction (Table III).

TABLE I. PATIENTS SURVIVING SURGICAL THERAPY FOR MECONIUM PERITONITIS DUE TO INTESTINAL ATRESIA

YEAR	AUTHOR	AGE AT OPERATION	ETIOLOGY	OPERATION
1943	Duncan[12]	60 hours	Multiple small bowel atresias	Resection and anastomosis, one-stage
1944	Neuhauser[25]	50 hours	Jejunal atresia	Anastomosis, side-to-side
1945	Arnheim[3]	28 hours	Ileal atresia	Resection and anastomosis, staged
1950	Lee[21]	65 hours	Transverse colon atresia	Staged operations
1949	Low[22]	4 days	Ileal atresia	Anastomosis, side-to-side
1951	Conrad[9]	22 hours	Jejunal atresia	Resection and anastomosis, one-stage
1954	Bentley[5]	6 days	Ileal atresia	Resection and anastomosis, one-stage
1954	Nixon[26]	4 days	Ileal atresia	Resection and anastomosis, one-stage
1954	Nixon[26]	14 hours	Ileal atresia	Resection and anastomosis, one-stage
1955	White[34]	3 days	Anal atresia	Perineal anoplasty, loop colostomy
1960	Authors	3 days	Ileal atresia	Resection and anastomosis, one-stage

TABLE II. PATIENTS SURVIVING SURGICAL THERAPY FOR MECONIUM PERITONITIS DUE TO OTHER CAUSES OF INTESTINAL OBSTRUCTION

YEAR	AUTHOR	AGE AT OPERATION	ETIOLOGY	OPERATION
1949	Hurwitt[20]	2½ hours	Mesenteric hernia	Staged operations
1950	Moretz[24]	52 hours	Volvulus	Resection and anastomosis, one-stage
1951	Doyle[11]	Not stated	Incarcerated hernia	Unknown
1952	May[23]	3 days	Mesenteric hernia	Resection and anastomosis
1952	Franklin[17]	Not stated	Meconium ileus	Unknown
1952	Forshall[15]	10 hours	Volvulus	Resection and anastomosis, one-stage
1954	Bentley[5]	Not stated	Volvulus	Unknown
1954	Connell[8]	2½ hours	Volvulus	Resection and anastomosis, one-stage
1956	Despirito[10]	26 hours	Pyloric diaphragm	Staged operations

TABLE III. PATIENTS SURVIVING SURGICAL THERAPY FOR MECONIUM PERITONITIS WITHOUT DEMONSTRABLE OBSTRUCTION

YEAR	AUTHOR	AGE AT OPERATION	ETIOLOGY	OPERATION
1943	Agarty[2]	56 hours	Unknown	Suture of ileal perforation
1949	Brunkow[7]	4 days	Unknown	Drainage of abscess
1950	Gover[18]	24 hours	Unknown	Suture of perforation
1951	Packard[28]	48 hours	Unknown	Drainage of abdomen
1951	Doyle[11]	Not stated	Unknown	Unknown
1952	Franklin[17]	Not stated	Unknown	Unknown
1952	Standard[32]	44 hours	Unknown	Transverse colostomy
1953	Bendel[4]	Not stated	Unknown	Unknown
1956	Weinberg[33]	5 days	Unknown	Lysis of adhesions
1957	Fox[16]	Not stated	Unknown	Perforation closed
1957	Fox[16]	Not stated	Unknown	No operation

The prolonged diarrhea demonstrated postoperatively by our patient is not unusual after extensive bowel resections in newborn infants. In an article reporting 2 such cases and reviewing the literature, Pilling and Cresson[29] reported the advantages of low-fat formula feeding. Compensatory changes in the remaining bowel to increase its absorptive surface have been reported in experimental animals[14] and are responsible for the gradual improvement noted.

SUMMARY

A case of meconium peritonitis complicating ileal atresia with successful surgical intervention and a 4-year follow-up is reported. Successfully treated patients in the medical literature are listed and categorized.

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Editorial

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Academic Tariff

The American physician traveling abroad today will be impressed by the widespread interest in American medicine and medical education. Even in a country such as India, which until recent years was oriented primarily to the British philosophy of education, one observes a growing desire on the part of many medical educators and physicians to study and adopt elements of the American educational system.

In the light of this interest it is tragic, to say the least, that there exists in America an "academic tariff" which thwarts the natural desire of the Indian graduate student to come to the United States for advanced clinical training. Specifically, this "tariff" is the denial to foreign students of the opportunity to sit for certain specialty board certifications. While it is true that for some specialties this privilege is granted, they are few in number and do not include the major specialties of medicine and surgery.

The academic tariff has produced results detrimental to the best interests of our nation and is beginning to damage our medical prestige abroad. In most instances the better students of India are going to the United Kingdom for graduate medical education, or, after training in the United States, some stop off in Canada or the British Isles to obtain appropriate and recognized degrees. In recent conversations with certain medical leaders in India there were implications that Americans are giving lip service to the universal bonds of medicine and at the same time are practicing restrictions on the free exchange of graduate education.

In medicine, as in politics, our nation has been thrust into a position of world leadership. Under these circumstances can we in medicine afford a provincialism which builds an artificial educational wall between nations? The continuation of such a narrow policy can only lead to a further questioning of our real interests in world medicine and an ultimate relinquishing by default of our leadership.

The Educational Council for Foreign Medical Graduates has been established recently in America to screen foreign applicants for graduate medical education in our hospitals. The candidate thus screened has an opportunity to continue specialty training in the same manner as his American or Canadian counterparts. It is difficult to understand why the foreign student thus qualified and permitted to train in an approved hospital is then denied the privilege of sitting for his certification. There is not a state in the Union

which issues a license to practice medicine on the basis of a specialty board certificate. In other words, obtaining certification cannot be interpreted as an indirect method of gaining the right to practice medicine in the United States or Canada. How, therefore, can the certification of a properly trained foreign specialist jeopardize American medicine?

The Medical Council of India, constituted by the Central Government, is the official body for the approval of medical qualifications, both undergraduate and graduate. At present this Council does not recognize American accreditation in medicine. With the understandable pride of a nation young in comparison to other autonomous nations, India has chosen to give due regard to reciprocity. This policy applies equally to all nations. For instance, the Council does not necessarily approve qualification merely on the basis of listing on the General Medical Council of the United Kingdom. Thus the Medical Council of India also has a responsibility in the ultimate solution of the problem of academic tariff.

This two-edged sword wreaks its vengeance on the hapless Indian student who would study graduate medicine in America. On one hand, even after completing his full term of clinical training in approved American or Canadian hospitals, in most instances he is not permitted certification; and on the other hand, should he by some means receive an American graduate clinical degree or certificate, it is not recognized in his own country! There is little wonder that the bright Indian student looks elsewhere than to the United States for medical education.

At this critical time in world history, particularly in the light of President Eisenhower's recent overwhelming and gracious welcome in India, we cannot afford to maintain the indecency of an artificial academic tariff. Such a situation not only restricts free international medical communications, but also seriously damages our status as leaders in the world of medicine.

A decisive step in the resolution of this matter would be a decision on the part of the specialty boards to establish certification for foreign physicians who have had their training in approved American and Canadian programs. A natural second step would then be to invite a representation from the Medical Council of India to assess American clinical gradute education. Such a mature and objective approach to the problem, carried out in the dispassionate atmosphere of academic good will, would yield results conducive to continued Indo-American cooperation and respect.

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